TITLE OF THE INVENTION

TYROSINE KINASE INHIBITORS

BACKGROUND OF THE INVENTION

Protein kinases (PKs) are enzymes that catalyze the phosphorylation of hydroxy groups on tyrosine, serine and threonine residues of proteins. The consequences of this seemingly simple activity are staggering; cell growth, differentiation and proliferation; i.e., virtually all aspects of cell life, in one way or another depend on PK activity. Furthermore, abnormal PK activity has been related to a host of disorders, ranging from relatively non life-threatening diseases such as psoriasis to extremely virulent diseases such as glioblastoma (brain cancer). PKs can be broken into two classes, the protein tyrosine kinases (PTKs) and the serine-threonine kinases (STKs).

Certain growth factor receptors exhibiting PK activity are known as receptor tyrosine kinases (RTKs). They comprise a large family of transmembrane receptors with diverse biological activity. As present, at least nineteen (19) distinct subfamilies of RTKs have been identified. One RTK subfamily contains the insulin receptor (IR), insulin-like growth factor I receptor (IGF-1R) and insulin receptor related receptor (IRR). IR and IGF-1R interact with insulin, IGF-I and IGF-II to activate a hetero-tetramer composed of two entirely extracellular glycosylated α subunits and two β subunits which cross the cell membrane and which contain the tyrosine kinase domain. The Insulin-like Growth Factor-1 Receptor (IGF-1R), and its ligands, IGF-1 and IGF-2, are abnormally expressed in numerous tumors, including, but not limited to, breast, prostate, thyroid, lung, hepatoma, colon, brain, neuroendocrine, and others.

A more complete listing of the known RTK subfamilies is described in Plowman et al., KN&P, 1994, 7(6) :334-339 which is incorporated by reference, including any drawings, as if fully set forth herein.

In addition to the RTKs, there also exists a family of entirely intracellular PTKs called "non-receptor tyrosine kinases" or "cellular tyrosine kinases." This latter designation, abbreviated "CTK", will be used herein. CTKs do not contain extracellular and transmembrane domains. At present, over 24 CTKs in 11 subfamilies (Src, Frk, Btk, Csk, Abl, Zap70, Fes, Fps, Fak, Jak and Ack) have been identified. The Src subfamily appears so far to be the largest group of CTKs and includes Src, Yes, Fyn, Lyn, Lck, Blk, Hck, Fgr and Yrk. For a more detailed

discussion of CTKs, see Bolen, Oncogene, 1993, 8:2025-2031, which is incorporated by reference, including any drawings, as if fully set forth herein.

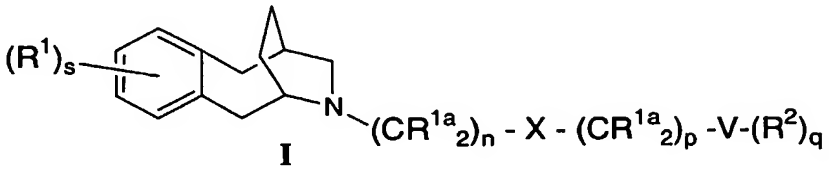
RTKs, CTKs and STKs have all been implicated in a host of pathogenic conditions including significantly, cancer. Other pathogenic conditions, which have been associated with PTKs include, without limitation, psoriasis, hepatic cirrhosis, diabetes, atherosclerosis, angiogenesis, restenosis, ocular diseases, rheumatoid arthritis and other inflammatory disorders, autoimmune diseases and a variety of renal disorders.

SUMMARY OF THE INVENTION

The present invention relates to compounds that are capable of inhibiting, modulating and/or regulating signal transduction of both receptor-type and non-receptor type tyrosine kinases. The compounds of the instant invention possess a core structure that comprises a benzazocine moiety. The present invention is also related to the pharmaceutically acceptable salts and stereoisomers of these compounds.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of this invention are useful in the inhibition of kinases and are illustrated by a compound of Formula I:



I

wherein

R^{1a} is independently selected from

1) H,
2) unsubstituted or substituted C_1-C_6 alkyl, and
3) OR^4;

R^{1b} is independently selected from

1) H, and

2) unsubstituted or substituted C_1-C_6 alkyl;

X is selected from

1) a bond,
2) C(O),
3) O, and
4) NR^4;

R^1 is independently selected from

1) H,
2) halo,
3) OR^4,
4) NO_2,
5) $-S(O)_mR^4$,
6) CN
7) unsubstituted or substituted C_1-C_{10} alkyl,
8) unsubstituted or substituted aryl,
9) unsubstituted or substituted C_2-C_6 alkenyl,
10) unsubstituted or substituted C_3-C_{10} cycloalkyl,
11) unsubstituted or substituted alkynyl,
12) unsubstituted or substituted heterocycle,
13) $-C(O)R^4$,
14) $C(O)OR^4$,
15) $C(O)N(R^4)_2$,
16) $S(O)_mN(R^4)_2$, and
17) $N(R^4)_2$;

V is selected from

1) H,
2) CF_3,
3) aryl,
4) heterocycle, and
5) C_3-C_{10} cycloalkyl;

R^2 is independently selected from

1) H,
2) unsubstituted or substituted C_1-C_{10} alkyl,
3) $-(CR^{1b})_tOR^4$,
4) Halo,
5) CN,
6) NO_2,
7) CF_3,
8) $-(CR^{1b})_tN(R^4)_2$,
9) $-C(O)OR^4$,
10) $-C(O)R^4$,
11) $-S(O)_2R^4$,
12) $-(CR^{1b})_tNR^4(CR^{1b})_tR^5$,
13) $-(CR^{1b})_tS(O)_mNR^4$,
14) $-C(O)OR^4R^5$,
15) $-NR^4C(O)R^4$,
16) unsubstituted or substituted aryl, and
17) unsubstituted or substituted heterocycle;

R^4 is independently selected from

1) H,
2) unsubstituted or substituted C_1-C_{10} alkyl,
3) unsubstituted or substituted C_3-C_{10} cycloalkyl,
4) unsubstituted or substituted aryl,
5) unsubstituted or substituted heterocycle, and
6) CF_3;

R^5 is independently selected from

1) unsubstituted or substituted aryl, and
2) unsubstituted or substituted heterocycle;

m is independently 0, 1 or 2;

n is 0 to 6;

p is 0 to 6;

q is 0 to 6, provided that when V is H or CF_3, q is 0; and

s is 0 to 16;

t is independently 0 to 6;

or a pharmaceutically acceptable salt or enantiomer thereof.

A second embodiment of the instant invention is a compound of Formula I, as described above, wherein R^{1b}, R^4, R^5 and variables m, n, p, q and t are as defined above and:

R^{1a} is independently selected from

1) H, and
2) unsubstituted or substituted C_1-C_6 alkyl;

X is selected from

1) a bond, and
2) C(O);

R^1 is independently selected from

1) H,
2) halo,
3) OR^4,
4) $N(R^4)_2$,
5) NO_2, and
6) unsubstituted or substituted C_1-C_{10} alkyl;

V is selected from

1) H,
2) CF_3,
3) aryl, and
4) heterocycle;

R^2 is independently selected from

1) H,

2) unsubstituted or substituted C_1-C_{10} alkyl,
3) $-(CR^{1b})_tOR^4$,
4) Halo,
5) CN,
6) NO_2,
7) CF_3,
8) $-(CR^{1b})_tN(R^4)_2$,
9) $-C(O)OR^4$,
10) $-(CR^{1b})_tS(O)_mNR^4$,
11) $-(CR^{1b})_tNR^4(CR^{1b})_tR^5$,
12) $-C(O)OR^4R^5$, and
13) $-NR^4C(O)R^4$;

s is 0 to 6;

or a pharmaceutically acceptable salt or stereoisomer thereof.

A further embodiment of the second embodiment is a compound of Formula I, as described above, wherein R^{1b}, X, R^1, R^2, R^4, R^5 and variables m, s and t are as defined above and:

R^{1a} is independently selected from
1) H, and
2) unsubstituted or substituted C_1-C_6 alkyl;

V is selected from
1) aryl, and
2) heterocycle;

n is 0 to 3;
p is 0 to 3;
q is 0 to 3;

or a pharmaceutically acceptable salt or stereoisomer thereof.

Examples of compounds of the instant invention include

(6*S*,9*R*)-12-(3-bromobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene;

(6*S*,9*R*)-12-(1*H*-indol-2-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene;

(6*S*,9*R*)-12-(3-chlorobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene;

(6S,9R)-12-(1H-indol-6-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[a][8]annulene;

(6S,9R)- 12-(3-bromobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo [*a*][8] annulen-4-amine;

(6*S*,9*R*)-12-(2-naphthylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene;

(6*S*,9*R*)-12-(1H-indol-7-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[a][8]annulene;

(6*S*,9*R*)-12-(3-methylbenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene;

(6*S*,9*R*)-12-[(4-bromo-1*H*-pyrrol-2-yl)methyl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene;

(6*S*,9*R*)-12-(1,3-benzodioxol-5-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene;

(6*S*,9*R*)-12-[3-(trifluoromethyl)benzyl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene;

(6*S*,9*R*)-12-benzyl-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene;

(6*S*,9*R*)-12-(3,5-dichlorobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene;

(6*S*,9*R*)-12-(3-nitrobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene;

(6*S*,9*R*)-12-[1-(3-bromophenyl)ethyl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene;

(6*S*,9*R*)-12-(3,4-dichlorobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene;

(6*S*,9*R*)-12-(3-fluorobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene;

(6*S*,9*R*)-4-bromo-12-(3-chlorobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene;

(6*S*,9*R*)-12-(1-naphthylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene;

(6*S*,9*R*)-12-(quinolin-3-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene;

(6*S*,9*R*)-12-(4-chlorobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene;

(6*S*,9*R*)-12-(3-methoxybenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene;

3-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulen-12-ylmethyl]benzonitrile;

(6*S*,9*R*)-12-[(5-bromothien-2-yl)methyl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene;

(6*S*,9*R*)-12-[(2-methoxy-1-naphthyl)methyl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene;

(6*S*,9*R*)-12-(4-methoxybenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene;

(6*S*,9*R*)-12-(1-benzothien-2-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene;

(6*S*,9*R*)-12-[(4,5-dibromothien-2-yl)methyl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene;

12-(4-chlorobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo [a][8]annulene;

(6*S*,9*R*)-12-[(5-methylthien-2-yl)methyl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene;

3-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulen-12-ylmethyl]aniline;

(6*S*,9*R*)-12-(1*H*-pyrrol-2-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene;

{2-bromo-4-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulen-12-ylmethyl]phenyl}methanol;

(6*S*,9*R*)-12-[(5-bromo-2-furyl)methyl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene;

(6*S*,9*R*)-12-(4-methylbenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene;

(6*S*,9*R*)-12-[(5-chloro-1*H*-indol-2-yl)methyl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene;

(6*R*,9*S*)-12-[(4-methoxy-1-naphthyl)methyl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene;

(6*S*,9*R*)-12-(1H-indol-5-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[a][8]annulene;

3-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulen-12-ylmethyl]phenol;

12-(3-bromobenzyl)-4-nitro-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene;

(6*S*,9*R*)-12-(thien-2-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene;

(6*S*,9*R*)-12-(1H-indol-4-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[a][8]annulene;

(6*S*,9*R*)-12-[(1*R*)-6-methoxy-2,3-dihydro-1H-inden-1-yl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene;

(6*S*,9*R*)-12-[(1*S*)-6-methoxy-2,3-dihydro-1H-inden-1-yl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene;

(6*S*,9*R*)-12-[(1*R*)-1-phenylethyl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[a][8]annulene;

(6*S*,9*R*)-12-[(1*S*)-1-phenylethyl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[a][8]annulene;

(6*S*,9*R*)-12-[(1*R*)-1-phenylethyl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[a][8]annulene;

(6*S*,9*R*)-12-[(1*S*)-1-phenylethyl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[a][8]annulene;

(6*S*,9*R*)-12-[(1*R*)-2,3-dihydro-1H-inden-1-yl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene;

(6*S*,9*R*)-12-[(1*S*)-2,3-dihydro-1H-inden-1-yl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene;

12-(3-bromobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8] annulen-3-amine;

2-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulen-12-ylmethyl]phenylamine;

12-(3-bromobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8] annulen-1-amine;

12-(4-chlorobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8] annulen-3-ol;

(6*S*,9*R*)-12-[(1-methyl-1,2,3,4-tetrahydroquinolin-6-yl)methyl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene;

4-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulen-12-ylmethyl]phenol;

(6*S*,9*R*)-12-[(5-methyl-2-furyl)methyl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene;

(6*S*,9*R*)-12-(1,1'-biphenyl-3-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene;

(6*S*,9*R*)-12-(quinolin-6-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene;

(6*S*,9*R*)-12-(1H-benzimidazol-2-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[a][8]annulene;

(6*S*,9*R*)-12-(quinolin-7-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene;

(6*S*,9*R*)-12-(isoquinolin-4-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene;

2-bromo-4-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8] annulen-12-ylmethyl]benzonitrile;

1-{2-bromo-4-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8] annulen-12-ylmethyl]phenyl}methanamine;

12-(4-methoxybenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8] annulen-3-ol;

4-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulen-12-ylmethyl]-2-methoxyphenol;

(6*S*,9*R*)-12-(2-phenylethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*] [8]annulene;

(6*S*,9*R*)-12-(2-chlorobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo [*a*][8]annulene;

(6*S*,9*R*)-12-[(1*R*)-1,2,3,4-tetrahydronaphthalen-1-yl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene;

(6*S*,9*R*)-12-[(1*S*)-1,2,3,4-tetrahydronaphthalen-1-yl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene;

3-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulen-12-ylmethyl]isoquinolin-1(2H)-one;

(6*S*,9*R*)-12-(4-nitrobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo [*a*][8]annulene;

(6*S*,9*R*)-12-(quinolin-8-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene;

(6*S*,9*R*)-12-(3-furylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo [*a*][8]annulene;

12-(3-bromobenzyl)-1-nitro-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo [*a*][8]annulene;

(6*R*,9*S*)-12-(3-chlorobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*] [8]annulene;

(6*S*,9*R*)-3-bromo-12-(3-chlorobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene;

(6*S*,9*R*)-12-(3,4-dimethoxybenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene;

(6*S*,9*R*)-12-{2-[(3*R*)-1-benzoyl-3-phenylpyrrolidin-3-yl]ethyl}-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene;

(6*S*,9*R*)-12-{2-[(3*S*)-1-benzoyl-3-phenylpyrrolidin-3-yl]ethyl}-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene;

(6*S*,9*R*)-12-[(1-methyl-1*H*-pyrrol-2-yl)methyl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene;

(6*S*,9*R*)-12-[(1-phenyl-1*H*-pyrazol-4-yl)methyl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene;

(6*S*,9*R*)-12-[(2-chloroquinolin-3-yl)methyl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene;

4-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulen-12-ylmethyl]benzonitrile;

(6*S*,9*R*)-12-[(1-methyl-1*H*-pyrazol-4-yl)methyl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene;

(6*S*,9*R*)-12-(quinolin-5-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene;

4-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulen-12-ylmethyl]phenylamine;

(6*S*,9*R*)-12-(3-phenylpropyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*] [8]annulene;

(6*R*,9*S*)-12-(5-phenylpentyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo [*a*][8]annulene;

(6*S*,9*R*)-12-(1*H*-pyrazol-5-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene;

(6*S*,9*R*)-12-(2-furylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*] [8]annulene;

(6*R*,9*S*)-12-(4-phenylbutyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*] [8]annulene;

(6*S*,9*R*)-12-[4-(trifluoromethoxy)benzyl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene;

(6*S*,9*R*)-12-[(5-methyl-1*H*-imidazol-2-yl)methyl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene;

(6*S*,9*R*)-12-(4-phenylbutyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*] [8]annulene;

(6*S*,9*R*)-12-(quinolin-2-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene;

{4-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulen-12-ylmethyl]phenyl}methanol;

(6*R*,9*S*)-12-(2-phenylethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*] [8]annulene;

methyl 2-bromo-4-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*] [8]annulen-12-ylmethyl]benzoate;

3-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulen-12-ylmethyl]quinolin-2(1H)-one;

12-(3-bromobenzyl)-3-nitro-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*] [8]annulene;

(6*S*,9*R*)-12-(isoquinolin-1-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene;

(6*S*,9*R*)-12-[(1*R*)-1-(3-bromophenyl)ethyl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene;

(6*S*,9*R*)-12-{2-[(3*R*)-3-phenyl-1-(phenylsulfonyl)pyrrolidin-3-yl]ethyl}-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene;

(6*S*,9*R*)-12-{2-[(3*S*)-3-phenyl-1-(phenylsulfonyl)pyrrolidin-3-yl]ethyl}-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene;

(6*S*,9*R*)-12-[(8-methoxyquinolin-2-yl)methyl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene;

(6*S*,9*R*)-12-(pyridin-3-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene;

N-{3-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulen-12-ylmethyl]phenyl}acetamide;

(6*S*,9*R*)-12-(quinolin-4-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene;

methyl 4-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulen-12-ylmethyl]benzoate;

(6*S*,9*R*)-12-(pyridin-4-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene;

(6*S*,9*R*)-12-(5-phenylpentyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo [*a*][8]annulene;

4-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulen-12-ylmethyl]benzylamine;

(6*R*,9*S*)-12-(3-phenylpropyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*] [8]annulene;

(6*R*,9*S*)-12-(2-naphthylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo [*a*][8]annulene;

(6*S*,9*R*)-12-{[5-(methoxymethyl)-2-furyl]methyl}-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene;

(6*R*,9*S*)-12-benzyl-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo [*a*][8]annulene;

(6*S*,9*R*)-12-(pyridin-2-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo [*a*][8]annulene;

(6*S*,9*R*)-12-hexyl-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene;

diethyl 5-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulen-12-ylmethyl]-3-methyl-1*H*-pyrrole-2,4-dicarboxylate;

N-{2-bromo-4-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8] annulen-12-ylmethyl]benzyl}-2-morpholin-4-ylethanamine;

(6*R*,9*S*)-12-hexyl-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene;

(6*R*,9*S*)-12-nonyl-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene;

(6*R*,9*S*)-12-(5-methylhexyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo [*a*][8]annulene;

(6*R*,9*S*)-12-(4-phenylbutanoyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo [a][8]annulene;

(6*S*,9*R*)-12-(1,1'-biphenyl-4-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene;

(6*R*,9*S*)-12-(2-chlorobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*] [8]annulene;

N-{4-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulen-12-ylmethyl]benzyl}-2-morpholin-4-ylethanamine;

12-(phenylacetyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulen-2-ol;

(6R,9S)-12-(4-chlorobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo [a][8]annulene;

4-[(6*R*,9*S*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulen-12-ylmethyl]phenol;

(6*R*,9*S*)-12-(4-methylbenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo [*a*][8]annulene;

(6*R*,9*S*)-12-ethyl-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene;

(6*S*,9*R*)-12-[(1*S*)-1-phenylethyl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo [a][8]annulene;

(6*S*,9*R*)-12-[(1*R*)-1-phenylethyl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo [a][8]annulene;

(6*R*,9*S*)-12-(4-methoxybenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo [*a*][8]annulene;

(6*S*,9*R*)-12-(1*H*-pyrazol-4-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene;

12-(4-chlorobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8] annulen-2-ol;

(6*S*,9*R*)-12-[(5-chloro-1H-indol-2-yl)carbonyl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene;

2-bromo-4-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8] annulen-12-ylmethyl]benzoic acid;

12-(2-phenylethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulen-2-ol;

(6*S*,9*R*)-12-(1,3-benzothiazol-2-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene;

1-{2-chloro-4-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*] [8]annulen-12-ylmethyl]phenyl}methanesulfonamide;

12-(4-methoxybenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8] annulen-2-ol;

(6*R*,9*S*)-12-butyl-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene;

(6*R*,9*S*)-12-isopentyl-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8] annulene;

2-morpholin-4-ylethyl 4-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulen-12-ylmethyl]benzoate;

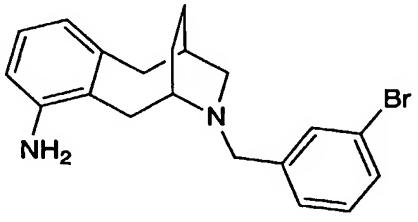
(6*S*,9*R*)-12-(4,4,4-trifluorobutyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene;

(6*R*,9*S*)-12-(4,4,4-trifluorobutyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene;

or the pharmaceutically acceptable salts or stereoisomers thereof.

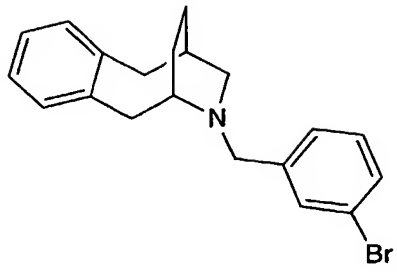
Specific examples of compounds of the instant invention include

(6S,9R)- 12-(3-bromobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo [*a*][8]annulen-4-amine

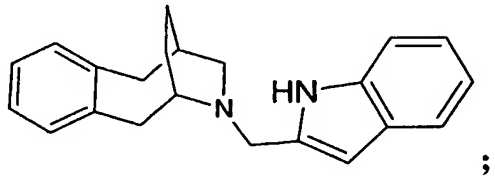


;

(6*S*,9*R*)-12-(3-bromobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene

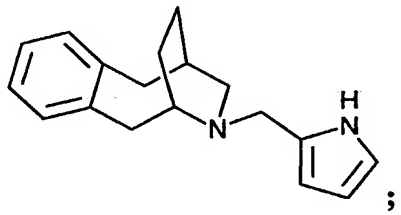


(6*S*,9*R*)-12-(1*H*-indol-2-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene



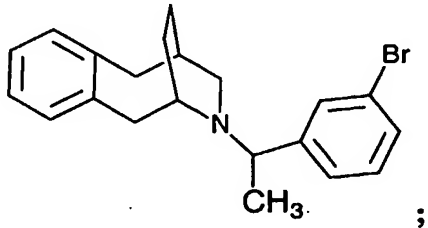
;

(6*S*,9*R*)-12-(1*H*-pyrrol-2-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene



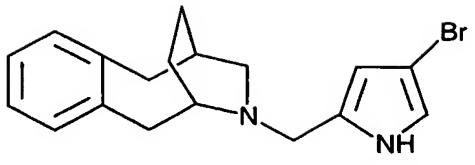
;

(6*S*,9*R*)-12-[1-(3-bromophenyl)ethyl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene



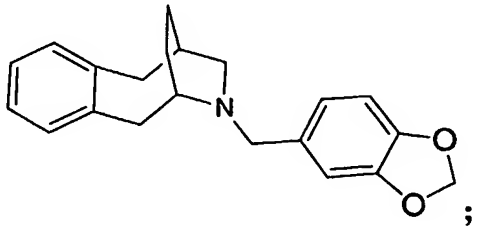
;

(6*S*,9*R*)-12-[(4-bromo-1*H*-pyrrol-2-yl)methyl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene



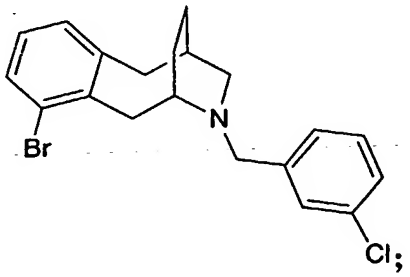
;

(6*S*,9*R*)-12-(1,3-benzodioxol-5-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene



;

(6*S*,9*R*)-4-bromo-12-(3-chlorobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene



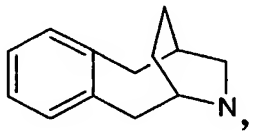
;

or the pharmaceutically acceptable salts or stereoisomers thereof.

The compounds of the present invention may have asymmetric centers, chiral axes, and chiral planes (as described in: E.L. Eliel and S.H. Wilen, *Stereochemistry of Carbon Compounds*, John Wiley & Sons, New York, 1994, pages 1119-1190), and occur as racemates, racemic mixtures, and as individual enantiomers and diastereomers, with all possible stereoisomers and mixtures thereof, including optical isomers, being included in the present invention. In addition, the compounds disclosed herein may exist as tautomers and both tautomeric forms are intended to be encompassed by the scope of the invention, even though only one tautomeric structure is depicted.

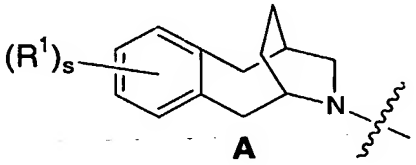
When any variable (e.g. aryl, heterocycle, R^1, R^a etc.) occurs more than one time in any substituent, its definition on each occurrence is independent at every other occurrence. Also, combinations of substituents and variables are permissible only if such combinations result in stable compounds.

Lines drawn into the ring systems from substituents (such as from R^2, R^3, etc.) indicate that the indicated bond may be attached to any of the substitutable ring carbon atoms or heteroatoms, including the carbon atom or heteroatom that is the point of attachment. If the ring system is polycyclic, such as



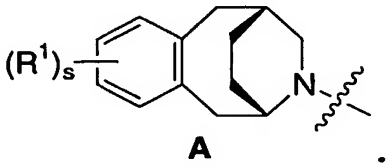
it is intended that the bond may be attached to any of the suitable carbon atoms or heteroatoms of any ring.

It is intended that moiety **A**, as illustrated in Formula **I**,



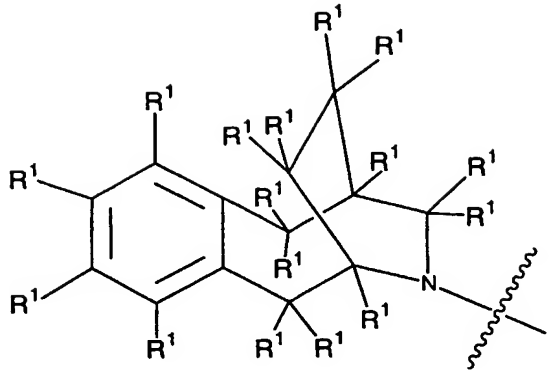
A

could also be represented as

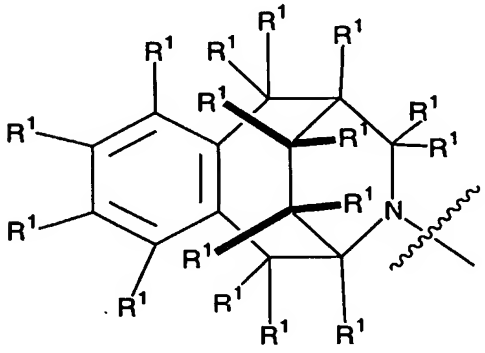


A

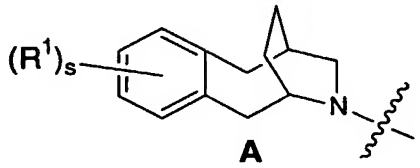
It is also intended that either of the above representations for moiety **A** could be further illustrated as follows:



or

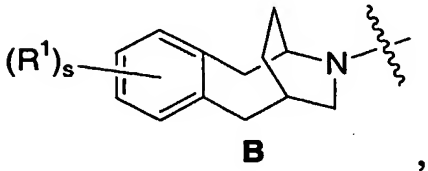


It should be noted that moiety **A**:



A

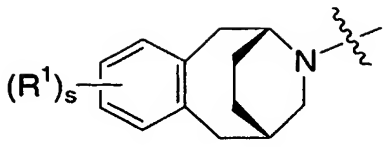
is an enantiomer of



B

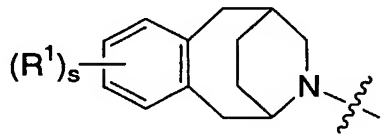
5 ,

and therefore moiety **A** and moiety **B** are stereoisomers. It should also be noted that moiety **B** could be represented as



and can be subsituted in a similar manner as illustrated for moiety **A**.

Additionally, the following structure

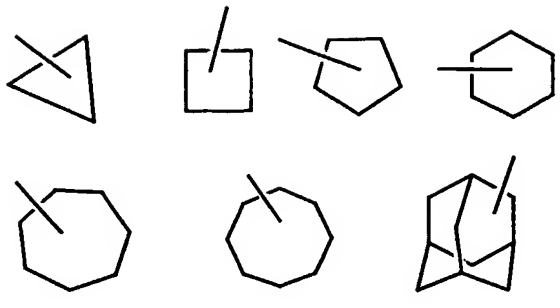


represents a racemic mixture of moiety **A** and moiety **B**.

It is understood that substituents and substitution patterns on the compounds of the instant invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art, as well as those methods set forth below, from readily available starting materials.

As used herein, "alkyl" is intended to include both branched, straight-chain, and cyclic saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For example, C_1-C_{10}, as in "C_1-C_{10} alkyl" is defined to include groups having 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbons in a linear or branched arrangement. For example, "C_1-C_{10} alkyl" specifically includes methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, adamantyl, and so on.

"Cycloalkyl" as used herein is intended to include non-aromatic cyclic hydrocarbon groups, having the specified number of carbon atoms, which may or may not be bridged or structurally constrained. Examples of such cycloalkyls include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, adamantyl, cyclooctyl, cycloheptyl, tetrahydro-naphthalene, methylenecylohexyl, and the like. As used herein, examples of "$C_3 - C_{10}$ cycloalkyl" may include, but are not limited to:



As used herein, the term "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge.

If no number of carbon atoms is specified, the term "alkenyl" refers to a non-aromatic hydrocarbon radical, straight, branched or cyclic, containing from 2 to 10 carbon atoms and at least one carbon to carbon double bond. Preferably one carbon to carbon double bond is present, and up to 4 non-aromatic carbon-carbon double bonds may be present. Thus, "C_2-C_6 alkenyl" means an alkenyl radical having from 2 to 6 carbon atoms. Alkenyl groups include ethenyl, propenyl, butenyl and cyclohexenyl. As described above with respect to alkyl, the straight, branched or cyclic portion of the alkenyl group may contain double bonds and may be substituted if a substituted alkenyl group is indicated.

The term "alkynyl" refers to a hydrocarbon radical straight, branched or cyclic, containing from 2 to 10 carbon atoms and at least one carbon to carbon triple bond. Up to 3 carbon-carbon triple bonds may be present. Thus, "C_2-C_6 alkynyl" means an alkynyl radical having from 2 to 6 carbon atoms. Alkynyl groups include ethynyl, propynyl and butynyl. As described above with respect to alkyl, the straight, branched or cyclic portion of the alkynyl group may contain triple bonds and may be substituted if a substituted alkynyl group is indicated.

As used herein, "aryl" is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 atoms in each ring, wherein at least one ring is aromatic. Examples of such aryl elements include phenyl, naphthyl, tetrahydronaphthyl, indanyl, indanonyl, biphenyl, tetralinyl, tetralonyl, fluorenonyl, phenanthryl, anthryl, acenaphthyl, tetrahydronaphthyl, and the like.

As appreciated by those of skill in the art, "halo" or "halogen" as used herein is intended to include chloro, fluoro, bromo and iodo.

The term heteroaryl, as used herein, represents a stable monocyclic or bicyclic ring of up to 7 atoms in each ring, wherein at least one ring is aromatic and

contains from 1 to 4 heteroatoms selected from the group consisting of O, N and S. Heteroaryl groups within the scope of this definition include but are not limited to: acridinyl, carbazolyl, cinnolinyl, quinoxalinyl, pyrrazolyl, indolyl, benzodioxolyl, benzotriazolyl, benzothiofuranyl, benzothiazolyl, furanyl, thienyl, benzothienyl, benzofuranyl, benzoquinolinyl, isoquinolinyl, oxazolyl, isoxazolyl, indolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, quinolinyl, tetrahydronaphthyl, tetrahydroquinoline, and the like.

The term heterocycle or heterocyclic or heterocyclyl, as used herein, represents a stable 5- to 7-membered monocyclic or stable 8- to 11-membered bicyclic heterocyclic ring which is either saturated or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O, and S, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. "Heterocycle" or "heterocyclyl" therefore includes the above mentioned heteroaryls, as well as dihydro and tetrathydro analogs thereof. Further examples of "heterocyclyl" include, but are not limited to the following: benzodioxolyl, benzofuranyl, benzofurazanyl, benzoimidazolyl, benzopyranyl, benzopyrazolyl, benzotriazolyl, benzothiazolyl, benzothienyl, benzothiofuranyl, benzothiophenyl, benzothiopyranyl, benzoxazolyl, carbazolyl, carbolinyl, chromanyl, cinnolinyl, diazapinonyl, dihydrobenzofuranyl, dihydrobenzofuryl, dihydrobenzoimidazolyl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrocyclopentapyridinyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidinyl, furyl, furanyl, imidazolyl, imidazolinyl, imidazolidinyl, imidazothiazolyl, imidazopyridinyl, indazolyl, indolazinyl, indolinyl, indolyl, isobenzofuranyl, isochromanyl, isoindolyl, isoindolinyl, isoquinolinone, isoquinolyl, isothiazolyl, isothiazolidinyl, isoxazolinyl, isoxazolyl, methylenedioxybenzoyl, morpholinyl, naphthpyridinyl, oxadiazolyl, oxazolyl, oxazolinyl, oxetanyl, oxoazepinyl, oxadiazolyl, oxodihydrophthalazinyl, oxodihydroindolyl, oxoimidazolidinyl, oxopiperazinyl, oxopiperdinyl, oxopyrrolidinyl, oxopyrimidinyl, oxopyrrolyl, oxotriazolyl, piperidyl, piperidinyl,

piperazinyl, pyranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridinonyl, pyridopyridinyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolyl, pyrrolidinyl, quinazolinyl, quinolinyl, quinolyl, quinolinonyl, quinoxalinyl, tetrahydrocycloheptapyridinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, tetrahydropyranyl, tetrahydroquinolinyl, tetrazolyl, tetrazolopyridyl, thiadiazolyl, thiazolyl, thiazolinyl, thienofuryl, thienyl, triazolyl, azetidinyl, 1,4-dioxanyl, hexahydroazepinyl, and the like. Preferably, heterocycle is selected from oxoazepinyl, benzimidazolyl, diazapinonyl, imidazolyl, oxoimidazolidinyl, indolyl, isoquinolinyl, morpholinyl, piperidyl, piperazinyl, pyridyl, pyrrolidinyl, oxopiperidinyl, oxopyrimidinyl, oxopyrrolidinyl, quinolinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, and thienyl.

As used herein, "aralkyl" is intended to mean an aryl moiety, as defined above, attached through a C_1-C_{10} alkyl linker, where alkyl is defined above. Examples of aralkyls include, but are not limited to, benzyl, naphthylmethyl and phenylpropyl.

As used herein, "heterocyclylalkyl" is intended to mean a heterocyclic moiety, as defined below, attached through a C_1-C_{10} alkyl linker, where alkyl is defined above. Examples of heterocyclylalkyls include, but are not limited to, pyridylmethyl, imidazolylethyl, pyrrolidinylmethyl, morpholinylethyl, quinolinylmethyl, imidazolylpropyl and the like.

As used herein, the terms "substituted C_1-C_{10} alkyl" and "substituted C_1-C_6 alkoxy" are intended to include the branch or straight-chain alkyl group of the specified number of carbon atoms, wherein the carbon atoms may be substituted with substituents selected from the group which includes, but is not limited to, halo, C_1-C_{20} alkyl, CF_3, NH_2, $N(C_1$-C_6 alkyl$)_2$, NO_2, oxo, CN, N_3, -OH, $-O(C_1$-C_6 alkyl), C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, (C_0-C_6 alkyl) $S(O)_{0\text{-}2}$-, (C_0-C_6 alkyl)$S(O)_{0\text{-}2}(C_0$-C_6 alkyl)-, (C_0-C_6 alkyl)C(O)NH-, H_2N-C(NH)-, $-O(C_1$-C_6 alkyl)CF_3, (C_0-C_6 alkyl)C(O)-, (C_0-C_6 alkyl)OC(O)-, (C_0-C_6 alkyl)$O(C_1$-C_6 alkyl)-, (C_0-C_6 alkyl)$C(O)_{1\text{-}2}(C_0$-C_6 alkyl)-, (C_0-C_6 alkyl)OC(O)NH-, aryl, aralkyl, heterocycle, heterocyclylalkyl, halo-aryl, halo-aralkyl, halo-heterocycle, halo-heterocyclylalkyl, cyano-aryl, cyano-aralkyl, cyano-heterocycle and cyano-heterocyclylalkyl.

As used herein, the terms "substituted C_3-C_{10} cycloalkyl", "substituted aryl", "substituted heterocycle", "substituted aralkyl" and "substituted heterocyclylalkyl" are intended to include the cyclic group containing from 1 to 3 substituents in addition to the point of attachment to the rest of the compound.

Preferably, the substituents are selected from the group which includes, but is not limited to, halo, C_1-C_{20} alkyl, CF_3, NH_2, $N(C_1$-C_6 alkyl$)_2$, NO_2, oxo, CN, N_3, -OH, -O(C_1-C_6 alkyl), C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, (C_0-C_6 alkyl) S(O)$_{0\text{-}2}$-, (C_0-C_6 alkyl)S(O)$_{0\text{-}2}$(C_0-C_6 alkyl)-, (C_0-C_6 alkyl)C(O)NH-, H_2N-C(NH)-, -O(C_1-C_6 alkyl)CF_3, (C_0-C_6 alkyl)C(O)-, (C_0-C_6 alkyl)OC(O)-, (C_0-C_6alkyl)O(C_1-C_6 alkyl)-, (C_0-C_6 alkyl)C(O)$_{1\text{-}2}$(C_0-C_6 alkyl)-, (C_0-C_6 alkyl) OC(O)NH-, aryl, aralkyl, heteroaryl, heterocyclylalkyl, halo-aryl, halo-aralkyl, halo-heterocycle, halo-heterocyclylalkyl, cyano-aryl, cyano-aralkyl, cyano-heterocycle and cyano-heterocyclylalkyl.

Preferably, R^1 is independently selected from H, unsubstituted or substituted C_1-C_{10} alkyl, $N(R^4)_2$, NO_2, OR^4, halo, -C(O)R^4, C(O)OR^4, and C(O)$N(R^4)_2$. Most preferably, R^1 is independently selected from H, $N(R^4)_2$, NO_2, OR^4, and halo.

Preferably, R^2 is independently selected from H, unsubstituted or substituted C_1-C_{10} alkyl, $-(CR^{1b})_tOR^4$, Halo, CN, NO_2, CF_3, $-(CR^{1b})_tN(R^4)_2$, $-C(O)OR^4$, $-C(O)R^4$,$-(CR^{1b})_tNR^4(CR^{1b})_tR^5$, $-(CR^{1b})_tS(O)_mNR^4$, $-C(O)OR^4R^5$, and $-NR^4C(O)R^4$.

Preferably, V is selected from aryl or heterocycle. More preferably, V is aryl. Most preferably, V is phenyl.

Preferably, X is selected from a bond, C(O) or O. Most preferably, X is a bond.

Preferably, n, p and q are independently 0, 1, 2, 3 or 4. More preferably, n is 0 or 1.

It is intended that the definition of any substituent or variable (e.g., R^1, R^{1a}, n, etc.) at a particular location in a molecule be independent of its definitions elsewhere in that molecule. Thus, -$N(R^4)_2$ represents -NHH, -$NHCH_3$, -NHC_2H_5, etc. It is understood that substituents and substitution patterns on the compounds of the instant invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art, as well as those methods set forth below, from readily available starting materials.

For use in medicine, the salts of the compounds of Formula I will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their pharmaceutically

acceptable salts. When the compound of the present invention is acidic, suitable "pharmaceutically acceptable salts" refers to salts prepared form pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as arginine, betaine caffeine, choline, N, N1-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine tripropylamine, tromethamine and the like.

When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric and tartaric acids.

The preparation of the pharmaceutically acceptable salts described above and other typical pharmaceutically acceptable salts is more fully described by Berg et al., "Pharmaceutical Salts," J. Pharm. Sci., 1977:66:1-19.

Included in the instant invention is the free form of compounds of Formula I, as well as the pharmaceutically acceptable salts and stereoisomers thereof. Some of the specific compounds exemplified herein are the protonated salts of amine compounds. The term "free form" refers to the amine compounds in non-salt form. The encompassed pharmaceutically acceptable salts not only include the salts exemplified for the specific compounds described herein, but also all the typical pharmaceutically acceptable salts of the free form of compounds of Formula I. The free form of the specific salt compounds described may be isolated using techniques known in the art. For example, the free form may be regenerated by treating the salt

with a suitable dilute aqueous base solution such as dilute aqueous NaOH, potassium carbonate, ammonia and sodium bicarbonate. The free forms may differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the acid and base salts are otherwise pharmaceutically equivalent to their respective free forms for purposes of the invention.

It will also be noted that the compounds of the present invention are potentially internal salts or zwitterions, since under physiological conditions a deprotonated acidic moiety in the compound, such as a carboxyl group, may be anionic, and this electronic charge might then be balanced off internally against the cationic charge of a protonated or alkylated basic moiety, such as a quaternary nitrogen atom.

Abbreviations, which may be used in the description of the chemistry and in the Examples that follow, include:

Ac_2O	Acetic anhydride;
AcOH	Acetic acid;
AIBN	2,2'-Azobisisobutyronitrile;
BINAP	2,2'-Bis(diphenylphosphino)-1,1' binaphthyl;
Bn	Benzyl;
BOC/Boc	*tert*-Butoxycarbonyl;
BSA	Bovine Serum Albumin;
CAN	Ceric Ammonia Nitrate;
CBz	Carbobenzyloxy;
CI	Chemical Ionization;
DBAD	Di-*tert*-butyl azodicarboxylate;
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene;
DCE	1,2-Dichloroethane;
DCM	Dichloromethane;
DIEA	*N,N*-Diisopropylethylamine;
DMAP	4-Dimethylaminopyridine;
DME	1,2-Dimethoxyethane;
DMF	*N,N*-Dimethylformamide;
DMSO	Methyl sulfoxide;
DPPA	Diphenylphosphoryl azide;
DTT	Dithiothreitol;

EDC	1-(3-Dimethylaminopropyl)-3-ethyl-carbodiimide-hydrochloride;
EDTA	Ethylenediaminetetraacetic acid;
ES	Electrospray;
ESI	Electrospray ionization;
Et_2O	Diethyl ether;
Et_3N	Triethylamine;
EtOAc	Ethyl acetate;
EtOH	Ethanol;
FAB	Fast atom bombardment;
HEPES	4-(2-Hydroxyethyl)-1-piperazineethanesulfonic acid;
HOAc	Acetic acid;
HOBT	1-Hydroxybenzotriazole hydrate;
HOOBT	3-Hydroxy-1,2,2-benzotriazin-4(3*H*)-one;
HPLC	High-performance liquid chromatography;
HRMS	High Resolution Mass Spectroscopy;
KOtBu	Potassium *tert*-butoxide;
LAH	Lithium aluminum hydride;
LCMS	Liquid Chromatography Mass Spectroscopy;
LiHMDS	Lithium bis(trimethylsilyl)amide;
MCPBA	*m*-Chloroperoxybenzoic acid;
Me	Methyl;
MeOH	Methanol;
Ms	Methanesulfonyl;
MS	Mass Spectroscopy;
MsCl	Methanesulfonyl chloride;
n-Bu	*n*-butyl;
n-Bu_3P	Tri-*n*-butylphosphine;
NaHMDS	Sodium bis(trimethylsilyl)amide;
NBS	*N*-Bromosuccinimide;
$Pd(PPh_3)_4$	Palladium tetrakis(triphenylphosphine);
$Pd_2(dba)_2$	Tris(dibenzylideneacetone)dipalladium (0)
Ph	phenyl;
PMSF	α-Toluenesulfonyl fluoride;
Py or pyr	Pyridine;
PYBOP	Benzotriazol-1-yloxytripyrrolidinophosphonium

(or PyBOP)	hexafluorophosphate;
RPLC	Reverse Phase Liquid Chromatography;
RT	Room Temperature;
t-Bu	*tert*-Butyl;
TBAF	Tetrabutylammonium fluoride;
TBSCl	*tert*-Butyldimethylsilyl chloride;
TFA	Trifluoroacetic acid;
THF	Tetrahydrofuran;
TIPS	Triisopropylsilyl;
TMS	Tetramethylsilane;
Tr	Trityl; and
Ts	Tosyl.

UTILITY

In another aspect, this present invention relates to a method of modulating the catalytic activity of PKs (protein kinases) in a mammal in need thereof comprising contacting the PK with a compound of Formula I.

As used herein, the term "modulation" or "modulating" refers to the alteration of the catalytic activity of receptor tyrosine kinases (RTKs), cellular tyrosine kinases (CTKs)and serine-threonine kinases (STKs). In particular, modulating refers to the activation of the catalytic activity of RTKs, CTKs and STKs, preferably the activation or inhibition of the catalytic activity of RTKs, CTKs and STKs, depending on the concentration of the compound or salt to which the RTKs, CTKs or STKs is exposed or, more preferably, the inhibition of the catalytic activity of RTKs, CTKs and STKs.

The term "catalytic activity" as used herein refers to the rate of phosphorylation of tyrosine under the influence, direct or indirect, of RTKs and/or CTKs or the phosphorylation of serine and threonine under the influence, direct or indirect, of STKs.

The term "contacting" as used herein refers to bringing a compound of this invention and a target PK together in such a manner that the compound can affect the catalytic activity of the PK, either directly; i.e., by interacting with the kinase itself, or indirectly; i.e., by interacting with another molecule on which the catalytic activity of the kinase is dependent. Such "contacting" can be accomplished "*in vitro,*"

i.e., in a test tube, a petri dish or the like. In a test tube, contacting may involve only a compound and a PK of interest or it may involve whole cells. Cells may also be maintained or grown in cell culture dishes and contacted with a compound in that environment. In this context, the ability of a particular compound to affect a PK related disorder; i.e., the IC_{50} of the compound, defined below, can be determined before use of the compounds *in vivo* with more complex living organisms is attempted. For cells outside the organism, multiple methods exist, and are well known to those skilled in the art, to get the PKs in contact with the compounds including, but not limited to, direct cell microinjection and numerous transmembrane carrier techniques.

The above-referenced PK is selected from the group comprising an RTK, a CTK or an STK in another aspect of this invention. Preferably, the PK is an RTK.

Furthermore, it is an aspect of this invention that the receptor tyrosine kinase (RTK) whose catalytic activity is modulated by a compound of this invention is selected from the group comprising EGF, HER2, HER3, HER4, IR, IGF-1R, IRR, PDGFRα, PDGFRβ, TrkA, TrkB, TrkC, HGF, CSFIR, C-Kit, C-fms, Flk-1R, Flk4, KDR/Flk-1, Flt-1, FGFR-1R, FGFR-1R, FGFR-3R and FGFR-4R. Preferably, the RTK is preferably, the receptor protein kinase is selected from IR, IGF-1R, or IRR.

In addition, it is an aspect of this invention that the cellular tyrosine kinase whose catalytic activity is modulated by a compound of this invention is selected from the group consisting of Src, Frk, Btk, Csk, Abl, ZAP70, Fes, Fps, Fak, Jak, Ack, Yes, Fyn, Lyn, Lck, Blk, Hck, Fgr and Yrk.

Another aspect of this invention is that the serine-threonine protein kinase whose catalytic activity is modulated by a compound of this invention is selected from the group consisting of CDK2 and Raf.

In another aspect, this invention relates to a method for treating or preventing a PK-related disorder in a mammal in need of such treatment comprising administering to the mammal a therapeutically effective amount of one or more of the compounds described above.

As used herein, "PK-related disorder," "PK driven disorder," and "abnormal PK activity" all refer to a condition characterized by inappropriate (i.e., diminished or, more commonly, exessive) PK catalytic activity, where the particular PK can be an RTK, a CTK or an STK. Inappropriate catalytic activity can arise as the result of either: (1) PK expression in cells which normally do not express PKs; (2)

increased PK expression leading to unwanted cell proliferation, differentiation and/or growth; or, (3) decreased PK expression leading to unwanted reductions in cell proliferation, differentiation and/or growth. Excessive-activity of a PK refers to either amplification of the gene encoding a particular PK or its ligand, or production of a level of PK activity which can correlate with a cell proliferation, differentiation and/or growth disorder (that is, as the level of the PK increases, the severity of one or more symptoms of a cellular disorder increase as the level of the PK activity decreases).

"Treat," "treating" or "treatment" with regard to a PK-related disorder refers to alleviating or abrogating the cause and/or the effects of a PK-related disorder.

As used herein, the terms "prevent", "preventing" and "prevention" refer to a method for barring a mammal from acquiring a PK-related disorder in the first place.

The term "administration" and variants thereof (e.g., "administering" a compound) in reference to a compound of the invention means introducing the compound or a prodrug of the compound into the system of the animal in need of treatment. When a compound of the invention or prodrug thereof is provided in combination with one or more other active agents (e.g., a cytotoxic agent, etc.), "administration" and its variants are each understood to include concurrent and sequential introduction of the compound or prodrug thereof and other agents.

The term "therapeutically effective amount" as used herein means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician.

The term "treating cancer" or "treatment of cancer" refers to administration to a mammal afflicted with a cancerous condition and refers to an effect that alleviates the cancerous condition by killing the cancerous cells, but also to an effect that results in the inhibition of growth and/or metastasis of the cancer.

The protein kinase-related disorder may be selected from the group comprising an RTK, a CTK or an STK-related disorder in a further aspect of this invention. Preferably, the protein kinase-related disorder is an RTK-related disorder.

In yet another aspect of this invention, the above referenced PK-related disorder may be selected from the group consisting of an EGFR-related disorder, a PDGFR-related disorder, an IGFR-related disorder and a flk-related disorder.

The above referenced PK-related disorder may be a cancer selected from, but not limited to, astrocytoma, basal or squamous cell carcinoma, brain cancer,

gliobastoma, bladder cancer, breast cancer, colorectal cancer, chrondrosarcoma, cervical cancer, adrenal cancer, choriocarcinoma, esophageal cancer, endometrial carcinoma, erythroleukemia, Ewing's sarcoma, gastrointestinal cancer, head and neck cancer, hepatoma, glioma, hepatocellular carcinoma, leukemia, leiomyoma, melanoma, non-small cell lung cancer, neural cancer, ovarian cancer, pancreatic cancer, prostate cancer, renal cell carcinoma, rhabdomyosarcoma, small cell lung cancer, thyoma, thyroid cancer, testicular cancer and osteosarcoma in a further aspect of this invention. More preferably, the PK-related disorder is a cancer selected from brain cancer, breast cancer, prostate cancer, colorectal cancer, small cell lung cancer, non-small cell lung cancer, renal cell carcinoma or endometrial carcinoma.

Included within the scope of the present invention is a pharmaceutical composition, which is comprised of a compound of Formula I as described above and a pharmaceutically acceptable carrier. The present invention also encompasses a method of treating or preventing cancer in a mammal in need of such treatment which is comprised of administering to said mammal a therapeutically effective amount of a compound of Formula I. Types of cancers which may be treated using compounds of Formula I include, but are not limited to, astrocytoma, basal or squamous cell carcinoma, brain cancer, gliobastoma, bladder cancer, breast cancer, colorectal cancer, chrondrosarcoma, cervical cancer, adrenal cancer, choriocarcinoma, esophageal cancer, endometrial carcinoma, erythroleukemia, Ewing's sarcoma, gastrointestinal cancer, head and neck cancer, hepatoma, glioma, hepatocellular carcinoma, leukemia, leiomyona, melanoma, non-small cell lung cancer, neural cancer, ovarian cancer, pancreatic cancer, prostate cancer, renal cell carcinoma, rhabdomyosarcoma, small cell lung cancer, thymona, thyroid cancer, testicular cancer and osteosarcoma in a further aspect of this invention. More preferably, the cancer being treated is selected from breast cancer, prostate cancer, colorectal cancer, small cell lung cancer, non-small cell lung cancer, renal cell carcinoma, or endometrial carcinoma.

The above-referenced PK-related disorder may be an IGFR-related disorder selected from diabetes, an autoimmune disorder, Alzheimer's and other cognitive disorders, a hyperproliferation disorder, aging, cancer, acromegaly, Crohn's disease, endometriosis, diabetic retinopathy, restenosis, fibrosis, psoriasis, osteoarthritis, rheumatoid arthritis, an inflammatory disorder and angiogenesis in yet another aspect of this invention.

A method of treating or preventing retinal vascularization which is comprised of administering to a mammal in need of such treatment a therapeutically

effective amount of compound of Formula I is also encompassed by the present invention. Methods of treating or preventing ocular diseases, such as diabetic retinopathy and age-related macular degeneration, are also part of the invention. Also included within the scope of the present invention is a method of treating or preventing inflammatory diseases, such as rheumatoid arthritis, psoriasis, contact dermatitis and delayed hypersensitivity reactions, as well as treatment or prevention of bone associated pathologies selected from osteosarcoma, osteoarthritis, and rickets.

Other disorders which might be treated with compounds of this invention include, without limitation, immunological and cardiovascular disorders such as atherosclerosis.

The invention also contemplates the use of the instantly claimed compounds in combination with a second compound selected from the group consisting of:

1) an estrogen receptor modulator,
2) an androgen receptor modulator,
3) retinoid receptor modulator,
4) a cytotoxic agent,
5) an antiproliferative agent,
6) a prenyl-protein transferase inhibitor,
7) an HMG-CoA reductase inhibitor,
8) an HIV protease inhibitor,
9) a reverse transcriptase inhibitor, and
10) angiogenesis inhibitor.

A preferred angiogenesis inhibitor is selected from the group consisting of a tyrosine kinase inhibitor, an inhibitor of epidermal-derived growth factor, an inhibitor of fibroblast-derived growth factor, an inhibitor of platelet derived growth factor, an MMP inhibitor, an integrin blocker, interferon-α, interleukin-12, pentosan polysulfate, a cyclooxygenase inhibitor, carboxyamidotriazole, combretastatin A-4, squalamine, 6-O-chloroacetyl-carbonyl)-fumagillol, thalidomide, angiostatin, troponin-1, and an antibody to VEGF. Preferred estrogen receptor modulators are tamoxifen and raloxifene.

Also included in the scope of the claims is a method of treating cancer, which comprises administering a therapeutically effective amount of a compound of Formula I in combination with a compound selected from the group consisting of:

1) an estrogen receptor modulator,

2) an androgen receptor modulator,
3) retinoid receptor modulator,
4) a cytotoxic agent,
5) an antiproliferative agent,
6) a prenyl-protein transferase inhibitor,
7) an HMG-CoA reductase inhibitor,
8) an HIV protease inhibitor,
9) a reverse transcriptase inhibitor, and
10) angiogenesis inhibitor.

And yet another embodiment is the method of treating cancer using the combination discussed above, in combination with radiation therapy.

And yet another embodiment of the invention is a method of treating cancer which comprises administering a therapeutically effective amount of a compound of Formula I in combination with paclitaxel or trastuzumab. The PKs whose catalytic activity is modulated by the compounds of this invention include protein tyrosine kinases of which there are two types, receptor tyrosine kinases (RTKs) and cellular tyrosine kinases (CTKs), and serine-threonine kinases (STKs). RTK-mediated signal transduction, is initiated by extracellular interaction with a specific growth factor (ligand), followed by receptor dimerization (or conformational changes in the case of IR, IGF-1R or IRR), transient stimulation of the intrinsic protein tyrosine kinase activity, autophosphorylation and subsequent phosphorylation of other substrate proteins. Binding sites are thereby created for intracellular signal transduction molecules and lead to the formation of complexes with a spectrum of cytoplasmic signaling molecules that facilitate the appropriate cellular response (e.g., cell division, metabolic effects on the extracellular microenvironment, etc.). See Schlessinger and Ullrich, 1992, Neuron 9:303-391.

It has been shown that tyrosine phosphorylation sites, on growth factor receptors, function as high-affinity binding sites for SH2 (src homology) domains of signaling molecules. Fantl et al., 1992, Cell 69:413-423; Songyang et al., 1994, Mol., Cell. Biol. 14:2777-2785); Songyang et al., 1993, Cell 72:767-778; and Koch et al., 1991, Science 252:668-678. Another signaling molecule domain, which interacts with phosphorylated tyrosines, is termed a PTB domain. Blaikie et al., 1994, J. Biol. Chem. 269:32031-32034; Gustafson et al., 1995, Mol. Cell Biol., 15:2500-25008; Kavanaugh and Williams, 1994, Science 266:1862-1865. Several intracellular substrate proteins that associate with RTKs have been identified. They may be

divided into two principal groups: (1) substrates which have a catalytic domain; and (2) substrates which lack such domain, but which serve as adapters and associate with catalytically active molecules. Songyang et al., 1993, Cell 72:767-778. The specificity of the interactions between receptors and SH2 domains of their substrates is determined by the amino acid residues immediately surrounding the phosphorylated tyrosine residue. Differences in the binding affinities between SH2 or PTB domains and the amino acid sequences surrounding the phosphotyrosine residues on particular receptors are consistent with the observed differences in their substrate phosphorylation profiles. Songyang et al., 1993, Cell 72:767-778. These observations suggest that the function of each RTK is determined not only by its pattern of expression and ligand availability, but also by the array of downstream signal transduction pathways that are activated by a particular receptor. Thus, phosphorylation provides an important regulatory step, which determines the selectivity of signaling pathways recruited by specific growth factor receptors, as well as differentiation factor receptors.

STKs, being primarily cytosolic, affect the internal biochemistry of the cell, often as a down-stream response to a PTK event. STKs have been implicated in the signaling process which initiates DNA synthesis and subsequent mitosis leading to cell proliferation.

Thus, PK signal transduction results in, among other responses, cell proliferation, differentiation, growth, metabolism, and cellular mobility. Abnormal cell proliferation may result in a wide array of disorders and diseases, including the development of neoplasia such as carcinoma, sarcoma, glioblastoma and hemangioma, disorders such as leukemia, psoriasis, arteriosclerosis, arthritis and diabetic retinopathy and other disorders related to uncontrolled angiogenesis and/or vasculogenesis.

A precise understanding of the mechanism by which the compounds of this invention inhibit PKs is not required in order to practice the present invention. However, while not hereby being bound to any particular mechanism or theory, it is believed that the compounds interact with the amino acids in the catalytic region of PKs. PKs typically possess a bi-lobate structure wherein ATP appears to bind in the cleft between the two lobes in a region where the amino acids are conserved among PKs. Inhibitors of PKs are believed to bind by non-covalent interactions such as hydrogen bonding, van der Waals forces and ionic interactions in the same general region where the aforesaid ATP binds to the PKs. The compounds disclosed herein

may have utility as *in vitro* assays for such proteins as well as exhibiting *in vivo* therapeutic effects through interaction with such proteins.

In another aspect, the protein kinase (PK), the catalytic activity of which is modulated by contact with a compound of this invention, is a protein tyrosine kinase (PTK), more particularly, a receptor protein tyrosine kinase (RTK). Among the RTKs whose catalytic activity can be modulated with a compound of this invention, or salt thereof, are, without limitation, EGF, HER2, HER3, HER4, IR, IGF-1R, IRR, PDGFRα, PDGFRβ, TrkA, TrkB, TrkC, HGF, CSFIR, C-Kit, C-fms, Flk-1R, Flk4, KDR/Flk-1, Flt-1, FGFR-1R, FGFR-2R, FGFR-3R and FGFR-4R. Most preferably, the RTK is selected from IGF-1R.

The protein tyrosine kinase whose catalytic activity is modulated by contact with a compound of this invention, or a salt or a prodrug thereof, can also be a non-receptor or cellular protein tyrosine kinase (CTK). Thus, the catalytic activity of CTKs such as, without limitation, Src, Frk, Btk, Csk, Abl, ZAP70, Fes, Fps, Fak, Jak, Ack, Yes, Fyn, Lyn, Lck, Blk, Hck, Fgr and Yrk, may be modulated by contact with a compound or salt of this invention.

Still another group of PKs which may have their catalytic activity modulated by contact with a compound of this invention are the serine-threonine protein kinases such as, without limitation, CDK2 and Raf.

This invention is also directed to compounds that modulate PK signal transduction by affecting the enzymatic activity of RTKs, CTKs and/or STKs, thereby interfering with the signals transduced by such proteins. More particularly, the present invention is directed to compounds which modulate RTK, CTK and/or STK mediated signal transduction pathways as a therapeutic approach to cure many kinds of solid tumors, including, but not limited to, carcinomas, sarcomas including Kaposi's sarcoma, erythroblastoma, glioblastoma, meningioma, astrocytoma, melonoma and myoblastoma. Treatment or prevention of non-solid tumor cancers such as leukemia are also contemplated by this invention. Indications may include, but are not limited to brain cancers, bladder cancers, ovarian cancers, gastric cancers, pancreatic cancers, colon cancers, blood cancers, breast cancers, prostrate cancers, renal cell carcinomas, lung cancer and bone cancers.

Further examples, without limitation, of the types of disorders related to inappropriate PK activity that the compounds described herein may be useful in preventing, treating and studying, are cell proliferative disorders, fibrotic disorders and metabolic disorders.

As previously mentioned, the Insulin-like Growth Factor-1 Receptor (IGF-1R) belongs to the family of transmembrane tyrosine kinase receptors such as platelet-derived growth factor receptor, the epidermal growth factor receptor, and the insulin receptor. There are two known ligands for the IGF-1R receptor. They are IGF-1 and IGF-2. As used herein, the term "IGF" refers to both IGF-1 and IGF-2. The insulin-like growth factor family of ligands, receptors and binding proteins is reviewed in Krywicki and Yee, *Breast Cancer Research and Treatment*, 22:7-19, 1992.

IGF/IGF-1R driven disorders are characterized by inappropriate or over-activity of IGF/IGF-1R. Inappropriate IGF activity refers to either: (1) IGF or IGF-1R expression in cells which normally do not express IGF or IGF-1R; (2) increased IGF or IGF-1R expression leading to unwanted cell proliferation such as cancer; (3) increased IGF or IGF-1R activity leading to unwanted cell proliferation, such as cancer; and/or over-activity of IGF or IGF-1R. Over-activity of IGF or IGF-1R refers to either an amplification of the gene encoding IGF-1, IGF-2, IGF-1R or the production of a level of IGF activity which can be correlated with a cell proliferative disorder (i.e., as the level of IGF increases the severity of one or more of the symptoms of the cell proliferative disorder increases) the bioavailability of IGF-1 and IGF-2 can also be affected by the presence or absence of a set of IGF binding presence or absence of a set of IGF binding proteins (IGF BPs) of which there are six know. Over activity of IGF/IGF-1R can also result from a down regulation of IGF-2 which contains an IGF-2 binding domain, but no intracellular kinase domain. Examples of IGF/IGF-1R driven disorders include the various IGF/IGF-1R related human malignancies reviewed in Cullen, *et al.*, *Cancer Investigation*, 9(4):443-454, 1991, incorporated herein by reference in its entirety, including any drawings. IGF/IGF-1Rs clinical importance and role in regulating osteoblast function is reviewed in Schmid, *Journal of Internal Medicine*, 234:535-542, 1993.

Thus, IGF-1R activities include: (1) phosphorylation of IGF-1R protein; (2) phosphorylation of an IGF-1R protein substrate; (3) interaction with an IGF adapter protein; (4) IGF-1R protein surface expression. Additional IGF-1R protein activities can be identified using standard techniques. IGF-1R activity can be assayed by measuring one or more of the following activities: (1) phosphorylation of IGF-1R; (2) phosphorylation of an IGF-1R substrate; (3) activation of an IGF-1R adapter molecule; and (4) activation of downstream signaling molecules, and/or

(5) increased cell division. These activities can be measured using techniques described below and known in the arts.

IGF-1R has been implicated as an absolute requirement for the establishment and maintenance of the transformed phenotype both *in vitro* and *in vivo* in several cell types (R. Baserga, *Cancer Research* 55:249-252, 1995). Herbimycin A has been said to inhibit the IGF-1R protein tyrosine kinase and cellular proliferation in human breast cancer cells (Sepp-Lorenzino, et al., 1994, *J. Cell Biochem. Suppl.* 18b: 246). Experiments studying the role of IGF-1R in transformation have used antisense strategies, dominant negative mutants, and antibodies to the IGF-1R and have led to the suggestion that IGR-1R may be a preferred target for therapeutic interventions.

IGF-1R, in addition to being implicated in nutritional support and in type-II diabetes, has also been associated with several types of cancers. For example, IGF-1 has been implicated as an autocrine growth stimulator for several tumor types, e.g. human breast cancer carcinoma cells (Arteago et al., J. Clin. Invest., 1989, 84:1418-1423) and small lung tumor cells (Macauley et al., Cancer Res., 1989, 50:2511-2517). In addition, IGF-1, while integrally involved in the normal growth and differentiation of the nervous system, also appears to be an autocrine stimulator of human gliomas. Sandberg-Nordqvist et al., Cancer Res., 1993, 53:2475-2478.

An example of IGF-2's protential involvement in colorectal cancer may be found in the up-regulation of IGF-2 mRNA in colon tumors relative to normal color tissue. (Zhang et al., Science (1997) 276:1268-1272.) IGF-2 may also play a role in hypoxia induced neovascularization of tumors. (Minet et al., Int. J. Mol. Med. (2000) 5:253-259.) IGF-2 may also play a role in tumorigenesis through activation of an insulin receptor isoform-A. IGF-2 activation of insulin receptor isoform-A activates cell survival signaling pathways in cells but its relative contribution to tumor cell growth and survival is unknown at this time. Insulin receptor isoform-A's kinase domain is identical to the standard insulin receptor's. Scalia et al., 2001, J. Cell Biochem. 82:610-618.

The importance of IGF-1R and its ligands in cell types in culture (fibroblasts, epithelial cells, smooth muscle cells, T-lymphocytes, myeloid cells, chondrocytes and osteoblasts (the stem cells of the bone marrow)) is illustrated by the ability of IGF-1 to stimulate cell growth and proliferation. Goldring and Goldring, Eukaryotic Gene Expression, 1991, 1:301-326. In a series of recent publications, Baserga and others suggests that IGF-1R plays a central role in the mechanism of transformation and, as such, could be a preferred target for therapeutic interventions

for a broad spectrum of human malignancies. Baserga, Cancer Res., 1995, 55:249-252; Baserga, Cell, 1994, 79:927-930; Coppola et al., Mol. Cell. Biol., 1994, 14:4588-4595; Baserga, Trends in Biotechnology, 1996, 14:150-152; H.M. Khandwala et al., Endocrine Reviews, 21:215-244, 2000. The predominant cancers that may be treated using a compound of the instant invention include, but are not limited to breast cancer, prostate cancer, colorectal cancer, small cell lung cancer, non-small cell lung cancer, renal cell carcinoma, or endometrial carcinoma.

IGF-1 has also been associated with retinal neovascularization. Proliferative diabetes retinopathy has been seen in some patients having high levels of IGF-1. (L.E. Smith et al., Nature Medicine, 1999, 5:1390-1395.)

Compounds of the instant invention may also be useful as anti-aging agents. It has been observed that there is a link between IGF signalling and aging. Experiments have shown that calorie-restricted mammals have low levels of insulin and IGF-1 and have a longer life span. Similar observations have been made for insects as well. (See C. Kenyon, Cell, 2001, 105:165-168; E. Strauss, Science, 2001, 292:41-43; K.D. Kimura et al., Science 1997, 277:942-946; M. Tatar et al., Science, 2001, 292:107-110).

STKs have been implicated in many types of cancer including, notably, breast cancer (Cance et al., Int. J. Cancer, 1993, 54:571-77).

The association between abnormal PK activity and disease is not restricted to cancer. For example, RTKs have been associated with diseases such as psoriasis, diabetes mellitus, endometriosis, angiogenesis, atheromatous plaque development, Alzheimer's disease, epidermal hyperproliferation, neurodegenerative diseases, age-related macular degeneration and hemangiomas. For example, EGFR has been indicated in corneal and dermal wound healing. Defects in Insulin-R and IGF-1R are indicated in type-II diabetes mellitus. A more complete correlation between specific RTKs and their therapeutic indications is set forth in Plowman et al., DN&P, 1994, 7:334-339.

As noted previously, not only RTKs but CTKs including, but not limited to, src, abl, fps, yes, fyn, lyn, lck, Zap70, blk, hck, fgr and yrk (reviewed by Bolen et al., FASEB J., 1993, 6:3403-3409) are involved in the proliferative and metabolic signal transduction pathway and thus could be expected, and have been shown, to be involved in may PTK-mediated disorders to which the present invention is directed. For example, mutated src (v-src) has been shown to be an oncoprotein ($pp60^{v\text{-}src}$) in chicken. Moreover, its cellular homolog, the protooncogene $pp60^{c\text{-}src}$

transmits oncogenic signals of many receptors. Over-expression of EGFR or HER2/neu in tumors leads to the constitutive activation of $pp60^{c\text{-}src}$, which is characteristic of malignant cells, but absent in normal cells. On the other hand, mice deficient in the expression of c-src exhibit an osteopetrotic phenotype, indicating a key participation of c-src in osteoclast function and a possible involvement in related disorders.

Similarly, Zap70 has been implicated in T-cell signaling which may relate to autoimmune disorders.

STKs have been associated with inflammation, autoimmune disease, immunoresponses, and hyperproliferation disorders such as restenosis, fibrosis, psoriasis, osteoarthritis and rheumatoid arthritis.

PKs have also been implicated in embryo implantation. Thus, the compounds of this invention may provide an effective method of preventing such embryo implantation and thereby be useful as birth control agents.

Finally, both RTKs and CTKs are currently suspected as being involved in hyperimmune disorders.

These and other aspects of the invention will be apparent from the teachings contained herein.

A method for identifying a chemical compound that modulates the catalytic activity of one or more of the above discussed protein kinases is another aspect of this invention. The method involved contacting cells expressing the desired protein kinase with a compound of this invention (or its salt or prodrug) and monitoring the cells for any effect that the compound has on them. The effect may be any observable, either to the naked eye or through the use of instrumentation, change or absence of change in a cell phenotype. The change or absence of change in the cell phenotype monitored may be, for example, without limitation, a change or absence of change in the catalytic activity of the protein kinase in the cells or a change or absence of change in the interaction of the protein kinase with a natural binding partner.

COMPOSITION

Pharmaceutical compositions of the above compounds are a further aspect of this invention.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

The present invention also encompasses a pharmaceutical composition useful in the treatment of cancer, comprising the administration of a therapeutically effective amount of the compounds of this invention, with or without pharmaceutically acceptable carriers or diluents. Suitable compositions of this invention include aqueous solutions comprising compounds of this invention and pharmacologically acceptable carriers, e.g., saline, at a pH level, e.g., 7.4. The solutions may be introduced into a patient's bloodstream by local bolus injection.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients, which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, microcrystalline cellulose, sodium crosscarmellose, corn starch, or alginic acid; binding agents, for example starch, gelatin, polyvinyl-pyrrolidone or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to mask the unpleasant taste of the drug or delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a water soluble taste masking material such as hydroxypropyl-methylcellulose or hydroxypropylcellulose, or a time delay material such as ethyl cellulose, cellulose acetate buryrate may be employed.

The compounds of the instant invention may also be co-administered with other well-known therapeutic agents that are selected for their particular usefulness against the condition that is being treated. For example, in the case of bone-related disorders, combinations that would be useful include those with antiresorptive bisphosphonates, such as alendronate and risedronate; integrin blockers (defined further below), such as $\alpha_v\beta_3$ antagonists; conjugated estrogens used in hormone replacement therapy, such as PREMPRO®, PREMARIN® and

ENDOMETRION®; selective estrogen receptor modulators (SERMs), such as raloxifene, droloxifene, CP-336,156 (Pfizer) and lasofoxifene; cathespin K inhibitors; and ATP proton pump inhibitors.

The instant compounds are also useful in combination with known anti-cancer agents. Such known anti-cancer agents include the following: estrogen receptor modulators, androgen receptor modulators, retinoid receptor modulators, cytotoxic agents, antiproliferative agents, prenyl-protein transferase inhibitors, HMG-CoA reductase inhibitors, HIV protease inhibitors, reverse transcriptase inhibitors, and other angiogenesis inhibitors. The instant compounds are particularly useful when coadminsitered with radiation therapy. The synergistic effects of inhibiting VEGF in combination with radiation therapy have been described in the art. (see WO 00/61186.)

"Estrogen receptor modulators" refers to compounds, which interfere or inhibit the binding of estrogen to the receptor, regardless of mechanism. Examples of estrogen receptor modulators include, but are not limited to, tamoxifen, raloxifene, idoxifene, LY353381, LY117081, toremifene, fulvestrant, 4-[7-(2,2-dimethyl-1-oxopropoxy-4-methyl-2-[4-[2-(1-piperidinyl)ethoxy]phenyl]-2H-1-benzopyran-3-yl]-phenyl-2,2-dimethylpropanoate, 4,4'-dihydroxybenzophenone-2,4-dinitrophenyl-hydrazone, and SH646.

"Androgen receptor modulators" refers to compounds which interfere or inhibit the binding of androgens to the receptor, regardless of mechanism. Examples of androgen receptor modulators include finasteride and other 5α-reductase inhibitors, nilutamide, flutamide, bicalutamide, liarozole, and abiraterone acetate.

"Retinoid receptor modulators" refers to compounds, which interfere or inhibit the binding of retinoids to the receptor, regardless of mechanism. Examples of such retinoid receptor modulators include bexarotene, tretinoin, 13-cis-retinoic acid, 9-cis-retinoic acid, α-difluoromethylornithine, ILX23-7553, trans-N-(4'-hydroxyphenyl) retinamide, and N-4-carboxyphenyl retinamide.

"Cytotoxic agents" refer to compounds which cause cell death primarily by interfering directly with the cell's functioning or inhibit or interfere with cell myosis, including alkylating agents, tumor necrosis factors, intercalators, microtubulin inhibitors, and topoisomerase inhibitors.

Examples of cytotoxic agents include, but are not limited to, tirapazimine, sertenef, cachectin, ifosfamide, tasonermin, lonidamine, carboplatin, doxorubicin, altretamine, prednimustine, dibromodulcitol, ranimustine, fotemustine,

nedaplatin, oxaliplatin, temozolomide, heptaplatin, estramustine, improsulfan tosilate, trofosfamide, nimustine, dibrospidium chloride, pumitepa, lobaplatin, satraplatin, profiromycin, cisplatin, irofulven, dexifosfamide, cis-aminedichloro(2-methyl-pyridine) platinum, benzylguanine, glufosfamide, GPX100, (trans, trans, trans)-bis-mu-(hexane-1,6-diamine)-mu-[diamine-platinum(II)]bis[diamine(chloro) platinum (II)]tetrachloride, diarizidinylspermine, arsenic trioxide, 1-(11-dodecylamino-10-hydroxyundecyl)-3,7-dimethylxanthine, zorubicin, idarubicin, daunorubicin, bisantrene, mitoxantrone, pirarubicin, pinafide, valrubicin, amrubicin, antineoplaston, 3'-deamino-3'-morpholino-13-deoxo-10-hydroxycarminomycin, annamycin, galarubicin, elinafide, MEN10755, and 4-demethoxy-3-deamino-3-aziridinyl-4-methylsulphonyl-daunorubicin (see WO 00/50032).

Examples of microtubulin inhibitors include paclitaxel, vindesine sulfate, 3',4'-didehydro-4'-deoxy-8'-norvincaleukoblastine, docetaxol, rhizoxin, dolastatin, mivobulin isethionate, auristatin, cemadotin, RPR109881, BMS184476, vinflunine, cryptophycin, 2,3,4,5,6-pentafluoro-N-(3-fluoro-4-methoxyphenyl) benzene sulfonamide, anhydrovinblastine, N,N-dimethyl-L-valyl-L-valyl-N-methyl-L-valyl-L-prolyl-L-proline-t-butylamide, TDX258, and BMS188797.

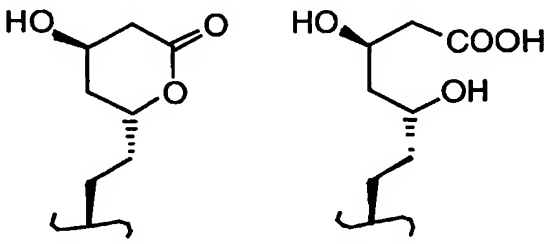
Some examples of topoisomerase inhibitors are topotecan, hycaptamine, irinotecan, rubitecan, 6-ethoxypropionyl-3',4'-O-exo-benzylidene-chartreusin, 9-methoxy-N,N-dimethyl-5-nitropyrazolo[3,4,5-kl]acridine-2-(6H) propanamine, 1-amino-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo[de]pyrano [3',4':b,7]indolizino[1,2b]quinoline-10,13(9H,15H)dione, lurtotecan, 7-[2-(N-isopropylamino)ethyl]-(20S)camptothecin, BNP1350, BNPI1100, BN80915, BN80942, etoposide phosphate, teniposide, sobuzoxane, 2'-dimethylamino-2'-deoxy-etoposide, GL331, N-[2-(dimethylamino)ethyl]-9-hydroxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide, asulacrine, (5a, 5aB, 8aa,9b)-9-[2-[N-[2-(dimethylamino)ethyl]-N-methylamino]ethyl]-5-[4-hydroxy-3,5-dimethoxyphenyl]-5,5a,6,8,8a,9-hexohydrofuro(3',4':6,7)naphtho(2,3-d)-1,3-dioxol-6-one, 2,3-(methylenedioxy)-5-methyl-7-hydroxy-8-methoxybenzo[c]-phenanthridinium, 6,9-bis[(2-aminoethyl)amino]benzo[g]isoguinoline-5,10-dione, 5-(3-aminopropylamino)-7,10-dihydroxy-2-(2-hydroxyethylaminomethyl)-6H-pyrazolo[4,5,1-de]acridin-6-one, N-[1-[2(diethylamino)ethylamino]-7-methoxy-9-oxo-9H-thioxanthen-4-ylmethyl] formamide, N-(2-(dimethylamino)ethyl)acridine-4-carboxamide, 6-[[2-(dimethylamino)ethyl]amino]-3-hydroxy-7H-indeno[2,1-c] quinolin-7-one, and dimesna.

"Antiproliferative agents" includes antisense RNA and DNA oligonucleotides such as G3139, ODN698, RVASKRAS, GEM231, and INX3001, and antimetabolites such as enocitabine, carmofur, tegafur, pentostatin, doxifluridine, trimetrexate, fludarabine, capecitabine, galocitabine, cytarabine ocfosfate, fosteabine sodium hydrate, raltitrexed, paltitrexid, emitefur, tiazofurin, decitabine, nolatrexed, pemetrexed, nelzarabine, 2'-deoxy-2'-methylidenecytidine, 2'-fluoromethylene-2'-deoxycytidine, N-[5-(2,3-dihydro-benzofuryl)sulfonyl]-N'-(3,4-dichlorophenyl)urea, N6-[4-deoxy-4-[N2-[2(E),4(E)-tetradecadienoyl]glycylamino]-L-glycero-B-L-manno-heptopyranosyl]adenine, aplidine, ecteinascidin, troxacitabine, 4-[2-amino-4-oxo-4,6,7,8-tetrahydro-3H-pyrimidino[5,4-b][1,4]thiazin-6-yl-(S)-ethyl]-2,5-thienoyl-L-glutamic acid, aminopterin, 5-flurouracil, alanosine, 11-acetyl-8-(carbamoyloxymethyl)-4-formyl-6-methoxy-14-oxa-1,11-diazatetracyclo(7.4.1.0.0)-tetradeca-2,4,6-trien-9-yl acetic acid ester, swainsonine, lometrexol, dexrazoxane, methioninase, 2'-cyano-2'-deoxy-N4-palmitoyl-1-B-D-arabino furanosyl cytosine, and 3-aminopyridine-2-carboxaldehyde thiosemicarbazone. "Antiproliferative agents" also includes monoclonal antibodies to growth factors, other than those listed under "angiogenesis inhibitors", such as trastuzumab, and tumor suppressor genes, such as p53, which can be delivered via recombinant virus-mediated gene transfer (see U.S. Patent No. 6,069,134, for example).

"HMG-CoA reductase inhibitors" refers to inhibitors of 3-hydroxy-3-methylglutaryl-CoA reductase. Compounds which have inhibitory activity for HMG-CoA reductase can be readily identified by using assays well-known in the art. For example, see the assays described or cited in U.S. Patent 4,231,938 at col. 6, and WO 84/02131 at pp. 30-33. The terms "HMG-CoA reductase inhibitor" and "inhibitor of HMG-CoA reductase" have the same meaning when used herein.

Examples of HMG-CoA reductase inhibitors that may be used include, but are not limited to, lovastatin (MEVACOR®, see U.S. Patent Nos. 4,231,938, 4,294,926 and 4,319,039); simvastatin (ZOCOR®, see U.S. Patent Nos. 4,444,784, 4,820,850 and 4,916,239); pravastatin (PRAVACHOL®, see U.S. Patent Nos. 4,346,227, 4,537,859, 4,410,629, 5,030,447 and 5,180,589); fluvastatin (LESCOL®, see U.S. Patent Nos. 5,354,772, 4,911,165, 4,929,437, 5,189,164, 5,118,853, 5,290,946 and 5,356,896); atorvastatin (LIPITOR®, see U.S. Patent Nos. 5,273,995, 4,681,893, 5,489,691 and 5,342,952); and cerivastatin (also known as rivastatin and BAYCHOL®, see US Patent No. 5,177,080). The structural formulae of these and additional HMG-CoA reductase inhibitors that may be used in the instant methods are

described at page 87 of M. Yalpani, "Cholesterol Lowering Drugs", *Chemistry & Industry*, pp. 85-89 (5 February 1996) and US Patent Nos. 4,782,084 and 4,885,314. The term HMG-CoA reductase inhibitor as used herein includes all pharmaceutically acceptable lactone and open-acid forms (i.e., where the lactone ring is opened to form the free acid) as well as salt and ester forms of compounds which have HMG-CoA reductase inhibitory activity, and therefor the use of such salts, esters, open-acid and lactone forms is included within the scope of this invention. An illustration of the lactone portion and its corresponding open-acid form is shown below as structures I and II.



Lactone I Open-Acid II

In HMG-CoA reductase inhibitors where an open-acid form can exist, salt and ester forms may preferably be formed from the open-acid, and all such forms are included within the meaning of the term "HMG-CoA reductase inhibitor" as used herein. Preferably, the HMG-CoA reductase inhibitor is selected from lovastatin and simvastatin, and most preferably simvastatin. Herein, the term "pharmaceutically acceptable salts" with respect to the HMG-CoA reductase inhibitor shall mean non-toxic salts of the compounds employed in this invention which are generally prepared by reacting the free acid with a suitable organic or inorganic base, particularly those formed from cations such as sodium, potassium, aluminum, calcium, lithium, magnesium, zinc and tetramethylammonium, as well as those salts formed from amines such as ammonia, ethylenediamine, N-methylglucamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chloroprocaine, diethanolamine, procaine, N-benzylphenethylamine, 1-p-chlorobenzyl-2-pyrrolidine-1'-yl-methylbenz-imidazole, diethylamine, piperazine, and tris(hydroxymethyl) aminomethane. Further examples of salt forms of HMG-CoA reductase inhibitors may include, but are not limited to, acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate,

dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynapthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylsulfate, mucate, napsylate, nitrate, oleate, oxalate, pamaote, palmitate, panthothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide, and valerate.

Ester derivatives of the described HMG-CoA reductase inhibitor compounds may act as prodrugs which, when absorbed into the bloodstream of a warm-blooded animal, may cleave in such a manner as to release the drug form and permit the drug to afford improved therapeutic efficacy.

"Prenyl-protein transferase inhibitor" refers to a compound which inhibits any one or any combination of the prenyl-protein transferase enzymes, including farnesyl-protein transferase (FPTase), geranylgeranyl-protein transferase type I (GGPTase-I), and geranylgeranyl-protein transferase type-II (GGPTase-II, also called Rab GGPTase). Examples of prenyl-protein transferase inhibiting compounds include (±)-6-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl) methyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone, (-)-6-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone, (+)-6-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl) methyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone, 5(S)-n-butyl-1-(2,3-dimethylphenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone, (S)-1-(3-chlorophenyl) -4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-5-[2-(ethanesulfonyl) methyl)-2-piperazinone, 5(S)-n-Butyl-1-(2-methylphenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone, 1-(3-chlorophenyl) -4-[1-(4-cyanobenzyl)-2-methyl-5-imidazolylmethyl]-2-piperazinone, 1-(2,2-diphenylethyl)-3-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl]piperidine, 4-{5-[4-hydroxymethyl-4-(4-chloropyridin-2-ylmethyl)-piperidine-1-ylmethyl]-2-methylimidazol-1-ylmethyl} benzonitrile, 4-{5-[4-hydroxymethyl-4-(3-chlorobenzyl)-piperidine-1-ylmethyl]-2-methylimidazol-1-ylmethyl}benzonitrile, 4-{3-[4-(2-oxo-2H-pyridin-1-yl)benzyl]-3H-imidazol-4-ylmethyl}benzonitrile, 4-{3-[4-(5-chloro-2-oxo-2H-[1,2']bipyridin-5'-ylmethyl]-3H-imidazol-4-ylmethyl}benzonitrile, 4-{3-[4-(2-oxo-2H-[1,2']bipyridin-5'-ylmethyl]-3H-imidazol-4-ylmethyl}benzonitrile, 4-[3-(2-oxo-1-phenyl-1,2-dihydropyridin-4-ylmethyl)-3H-imidazol-4-ylmethyl}benzonitrile, 18,19-dihydro-19-oxo-5*H*,17*H*-6,10:12,16-dimetheno-1H-imidazo[4,3-*c*][1,11,4]dioxaazacyclo -

nonadecine-9-carbonitrile, (±)-19,20-dihydro-19-oxo-5*H*-18,21-ethano-12,14-etheno-6,10-metheno-22*H*-benzo[*d*]imidazo[4,3-*k*][1,6,9,12]oxatriaza-cyclooctadecine-9-carbonitrile, 19,20-dihydro-19-oxo-5*H*,17*H*-18,21-ethano-6,10:12,16-dimetheno-22*H*-imidazo[3,4-*h*][1,8,11,14]oxatriazacycloeicosine-9-carbonitrile, and (±)-19,20-dihydro-3-methyl-19-oxo-5*H*-18,21-ethano-12,14-etheno-6,10-metheno-22*H*-benzo [*d*]imidazo[4,3-*k*][1,6,9,12]oxa-triazacyclooctadecine-9-carbonitrile.

Other examples of prenyl-protein transferase inhibitors can be found in the following publications and patents: WO 96/30343, WO 97/18813, WO 97/21701, WO 97/23478, WO 97/38665, WO 98/28980, WO 98/29119, WO 95/32987, U.S. Patent No. 5,420,245, U.S. Patent No. 5,523,430, U.S. Patent No. 5,532,359, U.S. Patent No. 5,510,510, U.S. Patent No. 5,589,485, U.S. Patent No. 5,602,098, European Patent Publ. 0 618 221, European Patent Publ. 0 675 112, European Patent Publ. 0 604 181, European Patent Publ. 0 696 593, WO 94/19357, WO 95/08542, WO 95/11917, WO 95/12612, WO 95/12572, WO 95/10514, U.S. Patent No. 5,661,152, WO 95/10515, WO 95/10516, WO 95/24612, WO 95/34535, WO 95/25086, WO 96/05529, WO 96/06138, WO 96/06193, WO 96/16443, WO 96/21701, WO 96/21456, WO 96/22278, WO 96/24611, WO 96/24612, WO 96/05168, WO 96/05169, WO 96/00736, U.S. Patent No. 5,571,792, WO 96/17861, WO 96/33159, WO 96/34850, WO 96/34851, WO 96/30017, WO 96/30018, WO 96/30362, WO 96/30363, WO 96/31111, WO 96/31477, WO 96/31478, WO 96/31501, WO 97/00252, WO 97/03047, WO 97/03050, WO 97/04785, WO 97/02920, WO 97/17070, WO 97/23478, WO 97/26246, WO 97/30053, WO 97/44350, WO 98/02436, and U.S. Patent No. 5,532,359. For an example of the role of a prenyl-protein transferase inhibitor on angiogenesis see European J. of Cancer, Vol. 35, No. 9, pp.1394-1401 (1999).

Examples of HIV protease inhibitors include amprenavir, abacavir, CGP-73547, CGP-61755, DMP-450, indinavir, nelfinavir, tipranavir, ritonavir, saquinavir, ABT-378, AG 1776, and BMS-232,632. Examples of reverse transcriptase inhibitors include delaviridine, efavirenz, GS-840, HB Y097, lamivudine, nevirapine, AZT, 3TC, ddC, and ddI.

"Angiogenesis inhibitors" refers to compounds that inhibit the formation of new blood vessels, regardless of mechanism. Examples of angiogenesis inhibitors include, but are not limited to, tyrosine kinase inhibitors, such as inhibitors of the tyrosine kinase receptors Flt-1 (VEGFR1) and Flk-1/KDR (VEGFR20), inhibitors of epidermal-derived, fibroblast-derived, or platelet derived growth factors,

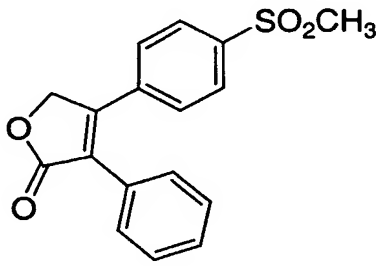
MMP (matrix metalloprotease) inhibitors, integrin blockers, interferon-α, interleukin-12, pentosan polysulfate, cyclooxygenase inhibitors, including nonsteroidal anti-inflammatories (NSAIDs) like aspirin and ibuprofen as well as selective cyclooxygenase-2 inhibitors like celecoxib and rofecoxib (PNAS, Vol. 89, p. 7384 (1992); JNCI, Vol. 69, p. 475 (1982); Arch. Opthalmol., Vol. 108, p.573 (1990); Anat. Rec., Vol. 238, p. 68 (1994); FEBS Letters, Vol. 372, p. 83 (1995); Clin, Orthop. Vol. 313, p. 76 (1995); J. Mol. Endocrinol., Vol. 16, p.107 (1996); Jpn. J. Pharmacol., Vol. 75, p. 105 (1997); Cancer Res., Vol. 57, p. 1625 (1997); Cell, Vol. 93, p. 705 (1998); Intl. J. Mol. Med., Vol. 2, p. 715 (1998); J. Biol. Chem., Vol. 274, p. 9116 (1999)), carboxyamidotriazole, combretastatin A-4, squalamine, 6-O-chloroacetyl-carbonyl)-fumagillol, thalidomide, angiostatin, troponin-1, angiotensin II antagonists (see Fernandez *et al.*, J. Lab. Clin. Med. 105:141-145 (1985)), and antibodies to VEGF. (see, Nature Biotechnology, Vol. 17, pp.963-968 (October 1999); Kim *et al.*, Nature, *362*, 841-844 (1993); WO 00/44777; and WO 00/61186).

As described above, the combinations with NSAID's are directed to the use of NSAID's which are potent COX-2 inhibiting agents. For purposes of this specification an NSAID is potent if it possess an IC_{50} for the inhibition of COX-2 of 1μM or less as measured by the cell or microsomal assay disclosed herein.

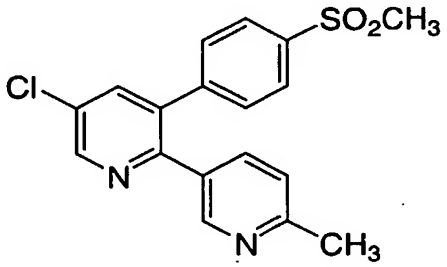
The invention also encompasses combinations with NSAID's which are selective COX-2 inhibitors. For purposes of this specification NSAID's which are selective inhibitors of COX-2 are defined as those which possess a specificity for inhibiting COX-2 over COX-1 of at least 100 fold as measured by the ratio of IC_{50} for COX-2 over IC_{50} for COX-1 evaluated by the cell or microsomal assay disclosed hereinunder. Such compounds include, but are not limited to those disclosed in U.S. 5,474,995, issued December 12, 1995, U.S. 5,861,419, issued January 19, 1999, U.S. 6,001,843, issued December 14, 1999, U.S. 6,020,343, issued February 1, 2000, U.S. 5,409,944, issued April 25, 1995, U.S. 5,436,265, issued July 25, 1995, U.S. 5,536,752, issued July 16, 1996, U.S. 5,550,142, issued August 27, 1996, U.S. 5,604,260, issued February 18, 1997, U.S. 5,698,584, issued December 16, 1997, U.S. 5,710,140, issued January 20,1998, WO 94/15932, published July 21, 1994, U.S. 5,344,991, issued June 6, 1994, U.S. 5,134,142, issued July 28, 1992, U.S. 5,380,738, issued January 10, 1995, U.S. 5,393,790, issued February 20, 1995, U.S. 5,466,823, issued November 14, 1995, U.S. 5,633,272, issued May 27, 1997, and U.S. 5,932,598, issued August 3, 1999, all of which are hereby incorporated by reference.

Inhibitors of COX-2 that are particularly useful in the instant method of treatment are:

3-phenyl-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone; and



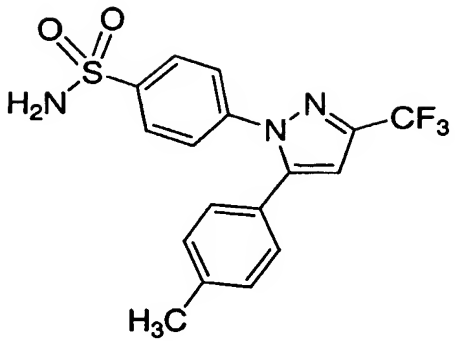
5-chloro-3-(4-methylsulfonyl)phenyl-2-(2-methyl-5-pyridinyl)pyridine;

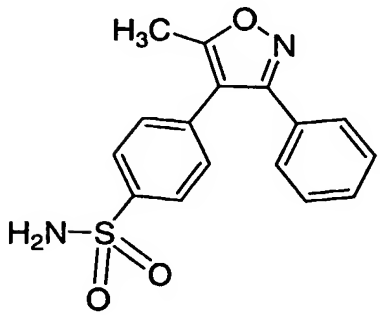


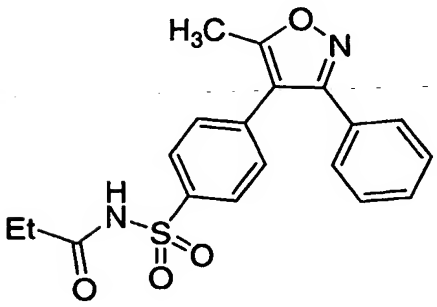
or a pharmaceutically acceptable salt thereof.

General and specific synthetic procedures for the preparation of the COX-2 inhibitor compounds described above are found in U.S. Patent No. 5,474,995, issued December 12, 1995, U.S. Patent No. 5,861,419, issued January 19, 1999, and U.S. Patent No. 6,001,843, issued December 14, 1999, all of which are herein incorporated by reference.

Compounds that have been described as specific inhibitors of COX-2 and are therefore useful in the present invention include, but are not limited to, the following:







or a pharmaceutically acceptable salt thereof.

Compounds, which are described as specific inhibitors of COX-2 and are therefore useful in the present invention, and methods of synthesis thereof, can be found in the following patents, pending applications and publications, which are herein incorporated by reference: WO 94/15932, published July 21, 1994, U.S. Patent No. 5,344,991, issued June 6, 1994, U.S. Patent No. 5,134,142, issued July 28, 1992, U.S. Patent No. 5,380,738, issued January 10, 1995, U.S. Patent No. 5,393,790, issued February 20, 1995, U.S. Patent No. 5,466,823, issued November 14, 1995, U.S. Patent No. 5,633,272, issued May 27, 1997, and U.S. Patent No. 5,932,598, issued August 3, 1999.

Compounds which are specific inhibitors of COX-2 and are therefore useful in the present invention, and methods of synthesis thereof, can be found in the following patents, pending applications and publications, which are herein incorporated by reference: U.S. Patent No. 5,474,995 issued December 12, 1995, U.S. Patent No. 5,861,419 issued January 19, 1999, U.S. Patent No. 6,001,843 issued December 14, 1999, U.S. Patent No. 6,020,343 issued February 1, 2000, U.S. Patent No. 5,409,944 issued April 25, 1995, U.S. Patent No. 5,436,265 issued July 25, 1995, U.S. Patent No. 5,536,752 issued July 16, 1996, U.S. Patent No. 5,550,142 issued August 27, 1996, U.S. Patent No. 5,604,260 issued February 18, 1997, U.S. Patent No. 5,698,584 issued December 16, 1997, and U.S. Patent No. 5,710,140 issued January 20,1998.

Other examples of angiogenesis inhibitors include, but are not limited to, endostation, ukrain, ranpirnase, IM862, 5-methoxy-4-[2-methyl-3-(3-methyl-2-butenyl)oxiranyl]-1-oxaspiro[2,5]oct-6-yl(chloroacetyl)carbamate, acetyldinanaline, 5-amino-1-[[3,5-dichloro-4-(4-chlorobenzoyl)phenyl]methyl]-1H-1,2,3-triazole-4-carboxamide,CM101, squalamine, combretastatin, RPI4610, NX31838, sulfated mannopentaose phosphate, 7,7-(carbonyl-bis[imino-N-methyl-4,2-pyrrolocarbonylimino[N-methyl-4,2-pyrrole]-carbonylimino]-bis-(1,3-naphthalene disulfonate), and 3-[(2,4-dimethylpyrrol-5-yl)methylene]-2-indolinone (SU5416).

As used above, "integrin blockers" refers to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the $\alpha_v\beta_3$ integrin, to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the $\alpha v\beta 5$ integrin, to compounds which antagonize, inhibit or counteract binding of a physiological ligand to both the $\alpha_v\beta_3$ integrin and the $\alpha_v\beta_5$ integrin, and to compounds which antagonize, inhibit or counteract the activity of the particular integrin(s) expressed on capillary endothelial cells. The term also refers to antagonists of the $\alpha v\beta_6$, $\alpha v\beta_8$, $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$ and $\alpha_6\beta_4$ integrins. The term also refers to antagonists of any combination of $\alpha v\beta_3$, $\alpha v\beta_5$, $\alpha v\beta_6$, $\alpha v\beta_8$, $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$ and $\alpha_6\beta_4$ integrins.

Some specific examples of tyrosine kinase inhibitors include N-(trifluoromethylphenyl)-5-methylisoxazol-4-carboxamide, 3-[(2,4-dimethylpyrrol-5-yl)methylidenyl)indolin-2-one, 17-(allylamino)-17-demethoxygeldanamycin, 4-(3-chloro-4-fluorophenylamino)-7-methoxy-6-[3-(4-morpholinyl)propoxyl]quinazoline, N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, BIBX1382, 2,3,9,10,11,12-hexahydro-10-(hydroxymethyl)-10-hydroxy-9-methyl-9,12-epoxy-1H-

diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocin-1-one, SH268, genistein, STI571, CEP2563, 4-(3-chlorophenylamino)-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidinemethane sulfonate, 4-(3-bromo-4-hydroxyphenyl)amino-6,7-dimethoxyquinazoline, 4-(4'-hydroxyphenyl)amino-6,7-dimethoxyquinazoline, SU6668, STI571A, N-4-chlorophenyl-4-(4-pyridylmethyl)-1-phthalazinamine, and EMD121974.

The instant compounds are also useful, alone or in combination with platelet fibrinogen receptor (GP IIb/IIIa) antagonists, such as tirofiban, to inhibit metastasis of cancerous cells. Tumor cells can activate platelets largely via thrombin generation. This activation is associated with the release of VEGF. The release of VEGF enhances metastasis by increasing extravasation at points of adhesion to vascular endothelium (Amirkhosravi, *Platelets* 10, 285-292, 1999). Therefore, the present compounds can serve to inhibit metastasis, alone or in combination with GP IIb/IIIa) antagonists. Examples of other fibrinogen receptor antagonists include abciximab, eptifibatide, sibrafiban, lamifiban, lotrafiban, cromofiban, and CT50352.

FORMULATIONS

The compounds of this invention may be administered to mammals, preferably humans, either alone or, preferably, in combination with pharmaceutically acceptable carriers, excipients or diluents, optionally with known adjuvants, such as alum, in a pharmaceutical composition, according to standard pharmaceutical practice. The compounds can be administered orally or parenterally, including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and/or topical routes of administration.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described below and the other pharmaceutically active agent(s) within its approved dosage range. Compounds of the instant invention may alternatively be used sequentially with known pharmaceutically acceptable agent(s) when a combination formulation is inappropriate.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water soluble carrier such as polyethyleneglycol or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

For oral use of a compound according to this invention, particularly for chemotherapy,the selected compound may be administered, for example, in the form of tablets or capsules, or as an aqueous solution or suspension. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch, and lubricating agents, such as magnesium stearate, are commonly added. For oral administration in capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring agents may be added. For intramuscular, intraperitoneal, subcutaneous and intravenous use, sterile solutions of the active ingredient are usually prepared, and the pH of the solutions should be suitably adjusted and buffered. For intravenous use, the total concentration of solutes should be controlled in order to render the preparation isotonic.

Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethylene-oxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as butylated hydroxyanisol or alpha-tocopherol.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, for example soy bean lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavoring agents, preservatives and antioxidants.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, flavoring and coloring agents and antioxidant.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous solution. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution.

The sterile injectable preparation may also be a sterile injectable oil-in-water microemulsion where the active ingredient is dissolved in the oily phase. For example, the active ingredient may be first dissolved in a mixture of soybean oil and lecithin. The oil solution then introduced into a water and glycerol mixture and processed to form a microemulation.

The injectable solutions or microemulsions may be introduced into a patient's bloodstream by local bolus injection. Alternatively, it may be advantageous to administer the solution or microemulsion in such a way as to maintain a constant circulating concentration of the instant compound. In order to maintain such a constant concentration, a continuous intravenous delivery device may be utilized. An example of such a device is the Deltec CADD-PLUS™ model 5400 intravenous pump.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension for intramuscular and subcutaneous administration. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents, which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butane diol. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Compounds of Formula I may also be administered in the form of a suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compound of Formula I are employed. (For purposes of this application, topical application shall include mouth washes and gargles.)

The compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles and delivery devices, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen. Compounds of the present invention may also be delivered as a suppository employing bases such as cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol.

Additionally, the compounds of the instant invention may be administered to a mammal in need thereof using a gel extrusion mechanism (GEM) device, such as that described in U.S. Patent No. 4,976,697, filed on December 11, 1990, which is hereby incorporated by reference.

When a compound according to this invention is administered into a human subject, the daily dosage will normally be determined by the prescribing

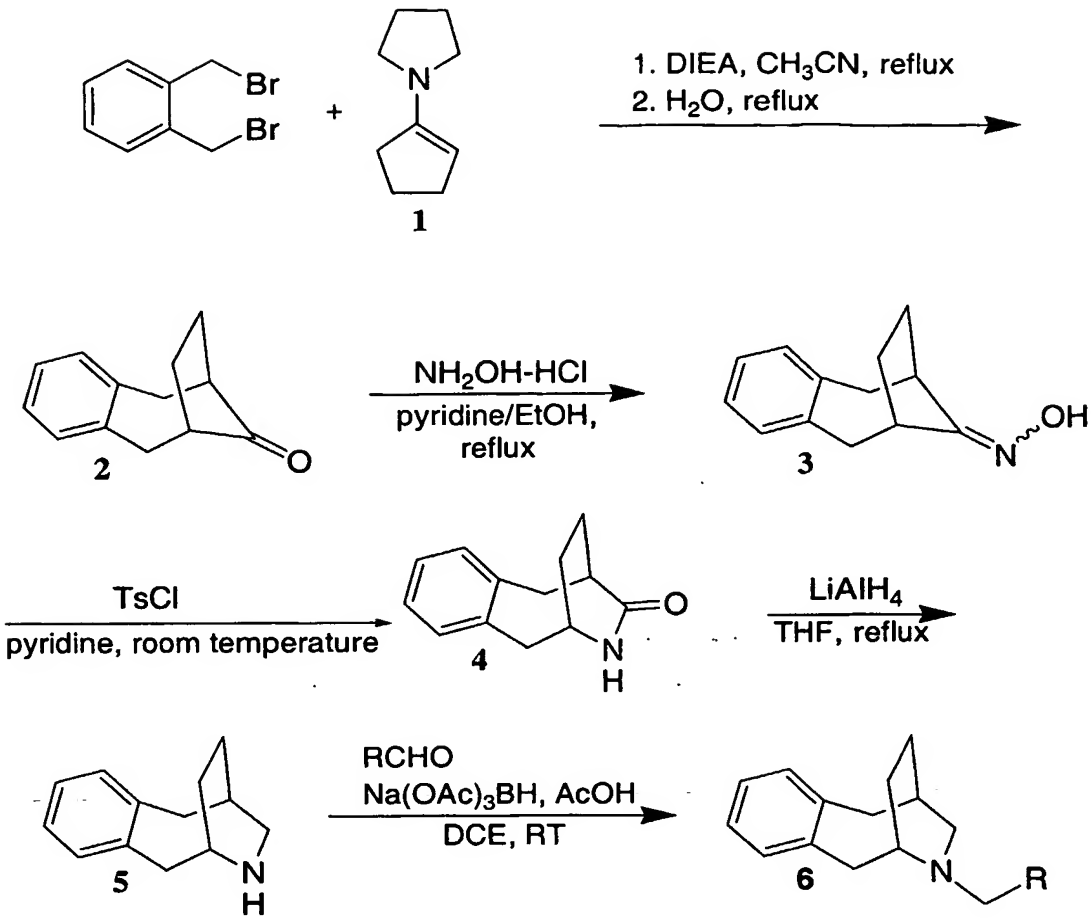
physician with the dosage generally varying according to the age, weight, and response of the individual patient, as well as the severity of the patient's symptoms.

In one exemplary application, a suitable amount of compound is administered to a mammal undergoing treatment for cancer. Administration occurs in an amount between about 0.1 mg/kg of body weight to about 60 mg/kg of body weight per day, preferably of between 0.5 mg/kg of body weight to about 40 mg/kg of body weight per day.

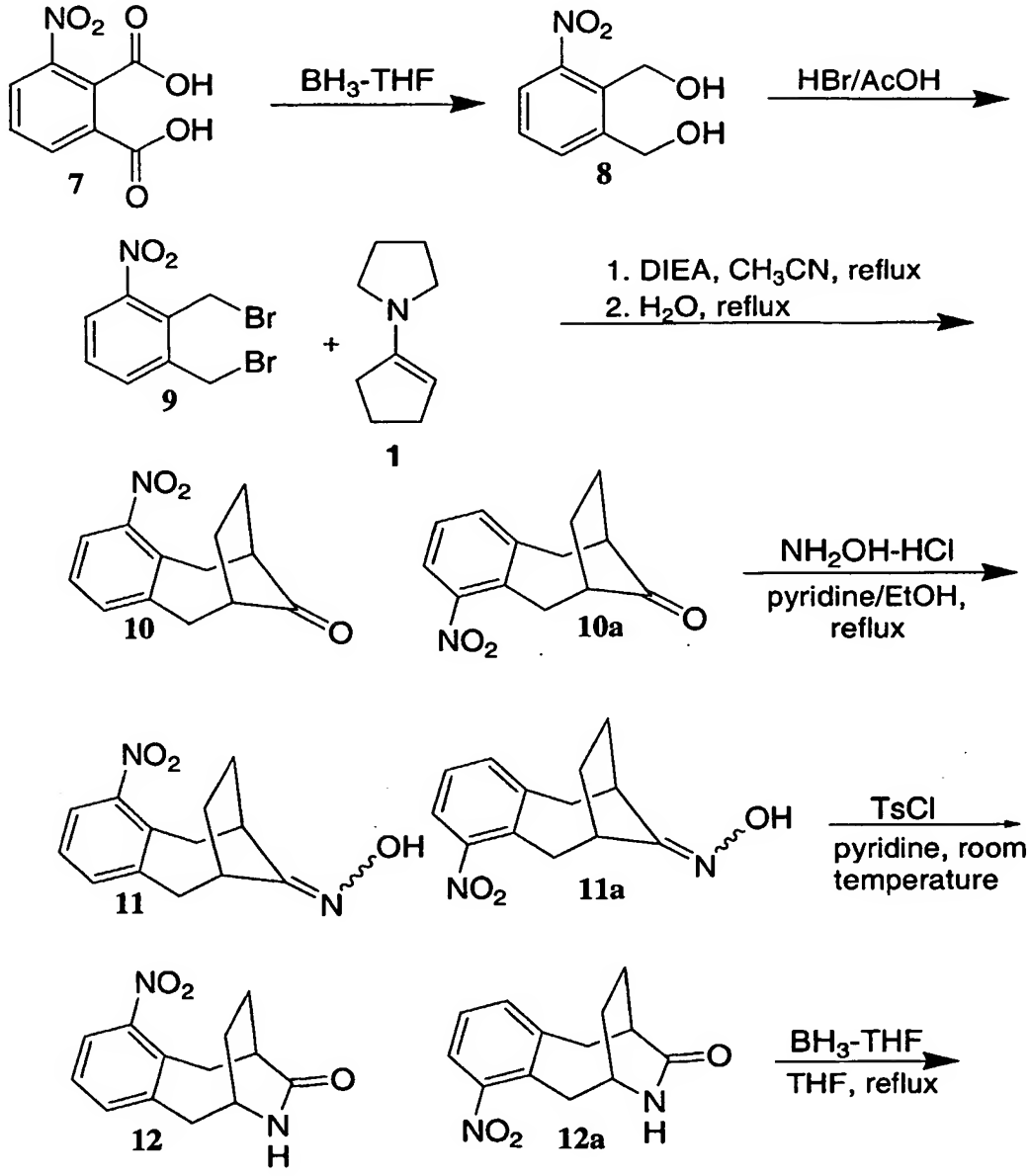
The compounds of this invention may be prepared by employing reactions as shown in the following schemes, in addition to other standard manipulations that are known in the literature or exemplified in the experimental procedures. It should be noted that, for the sake of brevity, only one enantiomer from the ring expansion is illustrated in the following schemes. Substitutions on the benzazocine moiety **A**, as illustrated hereinabove, other than those specifically exemplified in the schemes, may be prepared using techniques known in the art or suitably substituted starting materials. These schemes, therefore, are not limited by the compounds depicted nor by any particular substituents employed for illustrative purposes. Substituent numbering, as shown in the schemes, does not necessarily correlate to that used in the claims.

In the Schemes below, it is understood that R represents $(CR^{1a}{}_2)_{n-1}$-X-$(CR^{1a}{}_2)_p$-V- $(R^2)_q$ and R' represents $(CR^{1a}{}_2)_p$-V- $(R^2)_q$ as defined in Formula I.

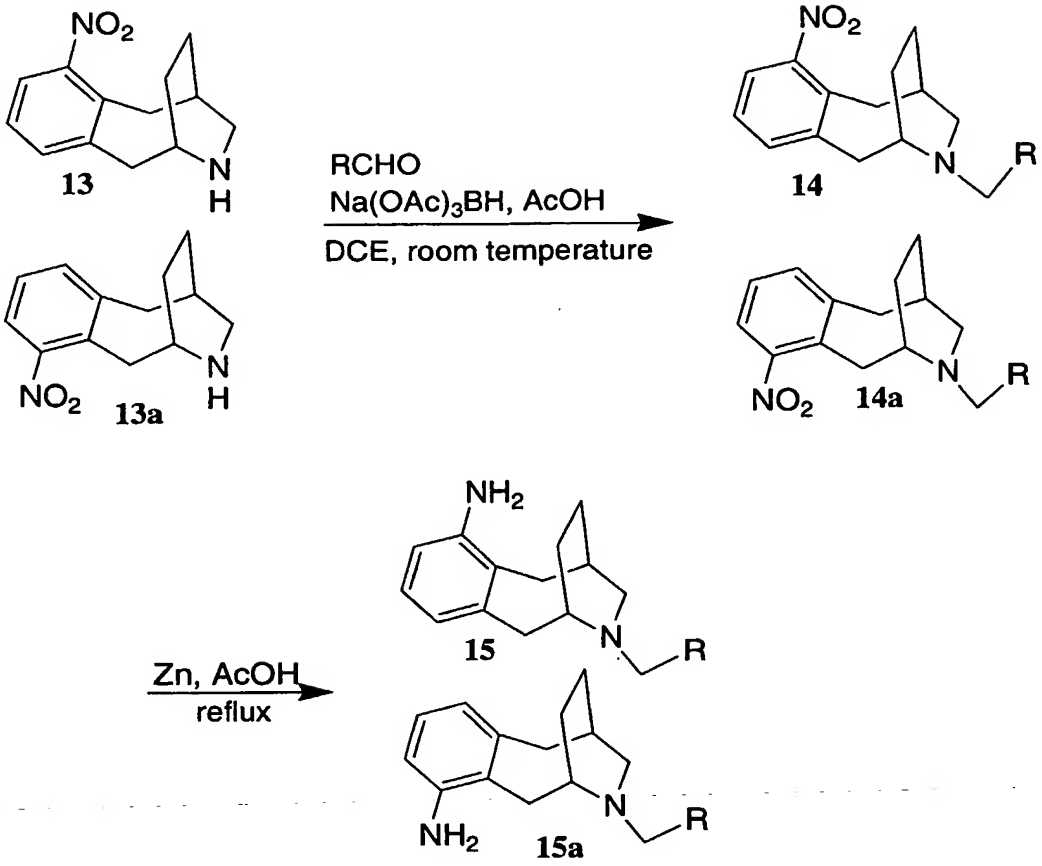
SCHEME 1


Br
Br
+
N
1
1. DIEA, CH3CN, reflux
2. H2O, reflux
2
O
NH2OH-HCl
pyridine/EtOH,
reflux
3
OH
N
TsCl
pyridine, room temperature
4
O
N
H
LiAlH4
THF, reflux
5
N
H
RCHO
Na(OAc)3BH, AcOH
DCE, RT
6
N
R

SCHEME 2


NO2
O
OH
OH
O
7
BH3-THF
NO2
OH
OH
8
HBr/AcOH
NO2
Br
Br
9
+
N
1
1. DIEA, CH3CN, reflux
2. H2O, reflux
NO2
10
O
NO2
10a
O
NH2OH-HCl
pyridine/EtOH,
reflux
NO2
OH
N
11
NO2
OH
N
11a
TsCl
pyridine, room
temperature
NO2
O
N
H
12
NO2
O
N
H
12a
BH3-THF
THF, reflux

SCHEME 2 (CONTD.)



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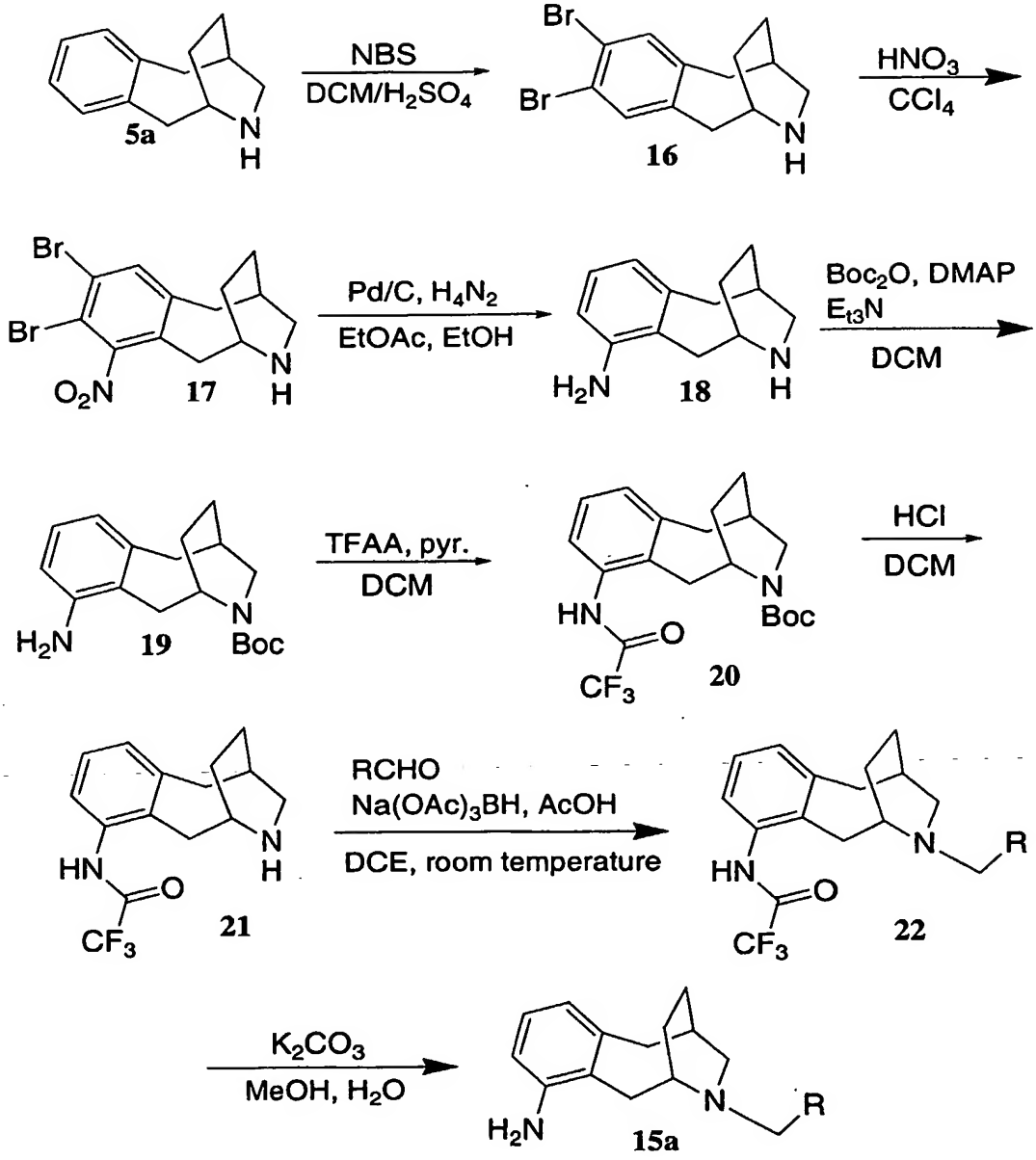
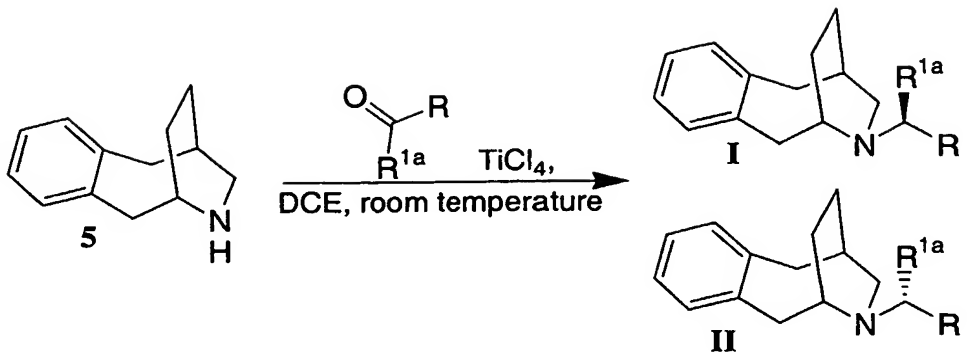

NBS
DCM/H2SO4
HNO3
CCl4
Pd/C, H4N2
EtOAc, EtOH
Boc2O, DMAP
Et3N
DCM
TFAA, pyr.
DCM
HCl
DCM
RCHO
Na(OAc)3BH, AcOH
DCE, room temperature
K2CO3
MeOH, H2O
5a
16
17
18
19
20
21
22
15a

SCHEME 4



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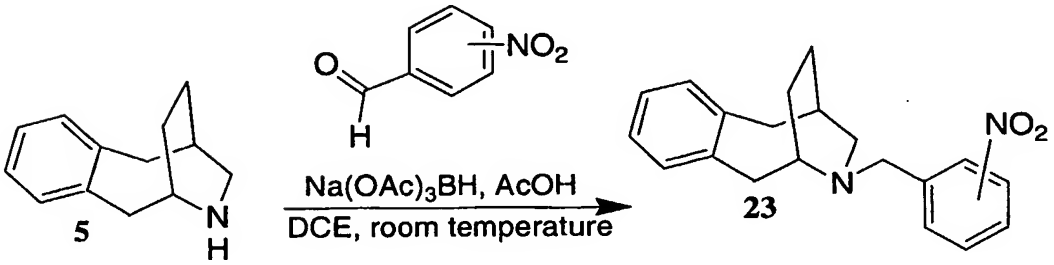

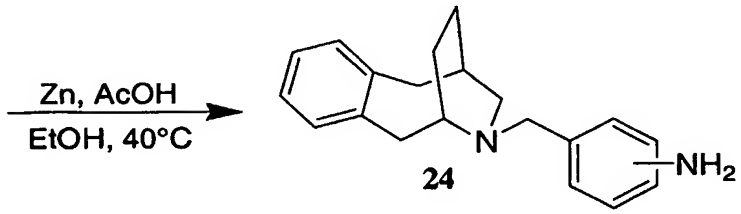

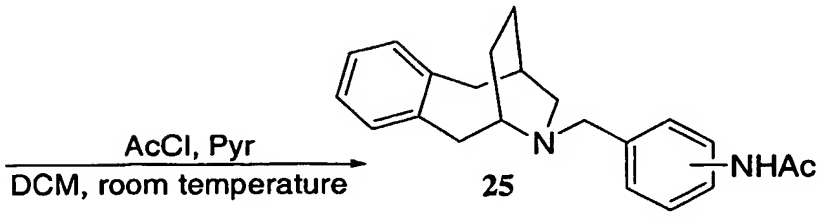

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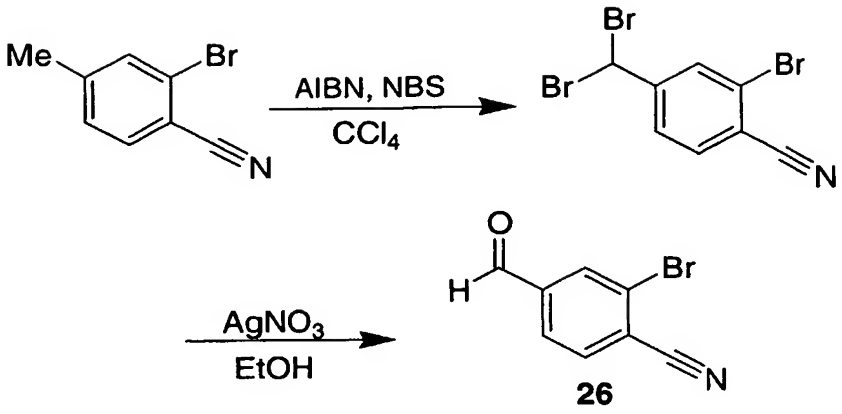
SCHEME 6



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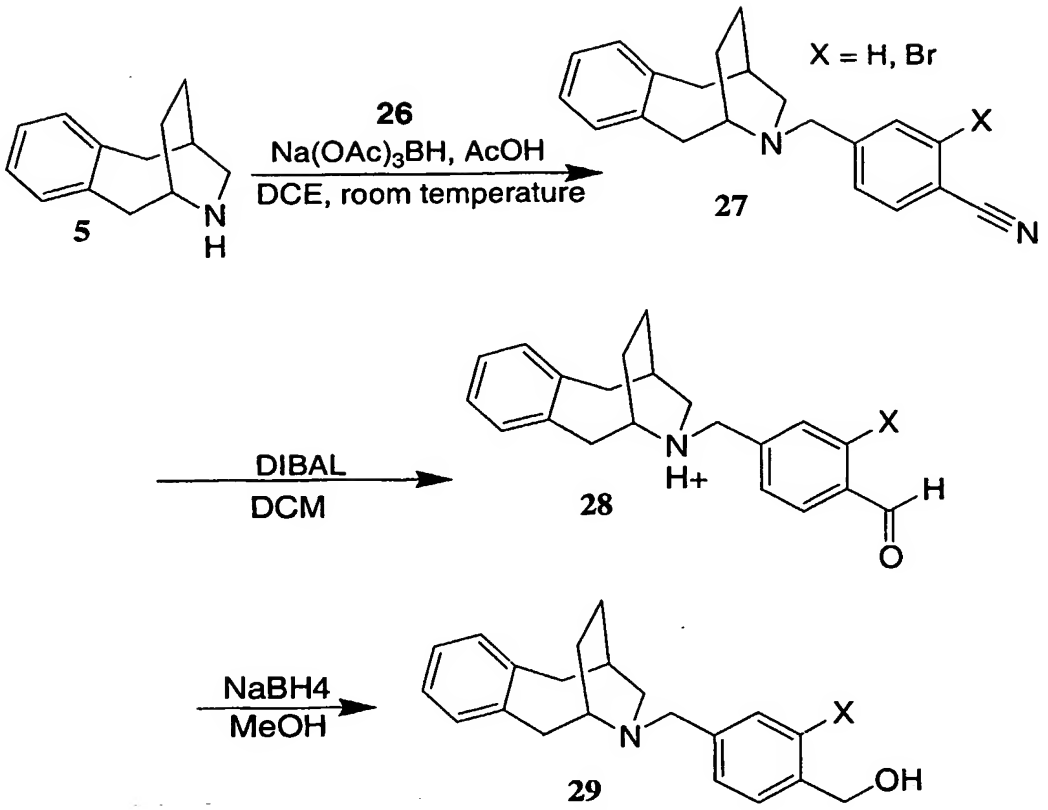
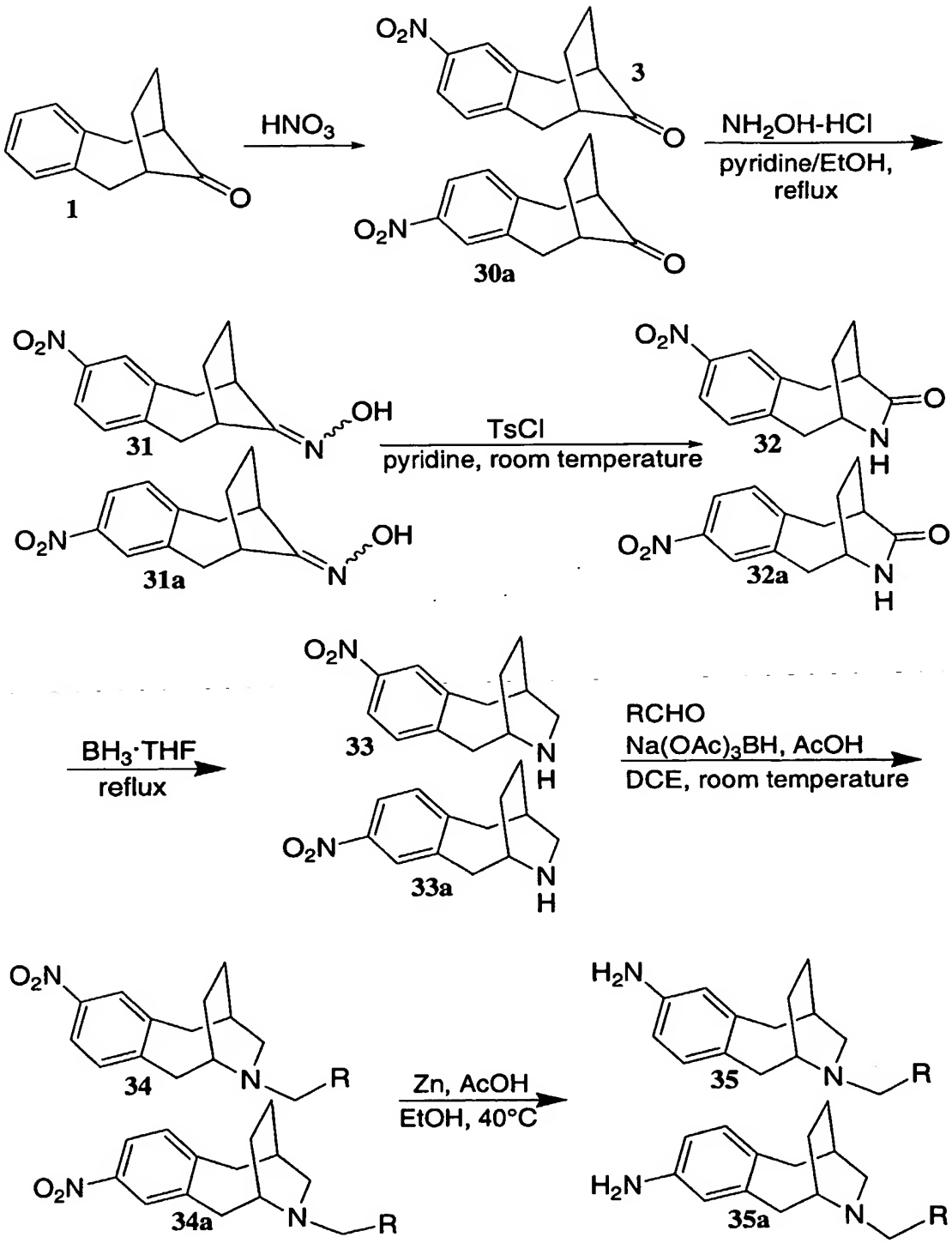
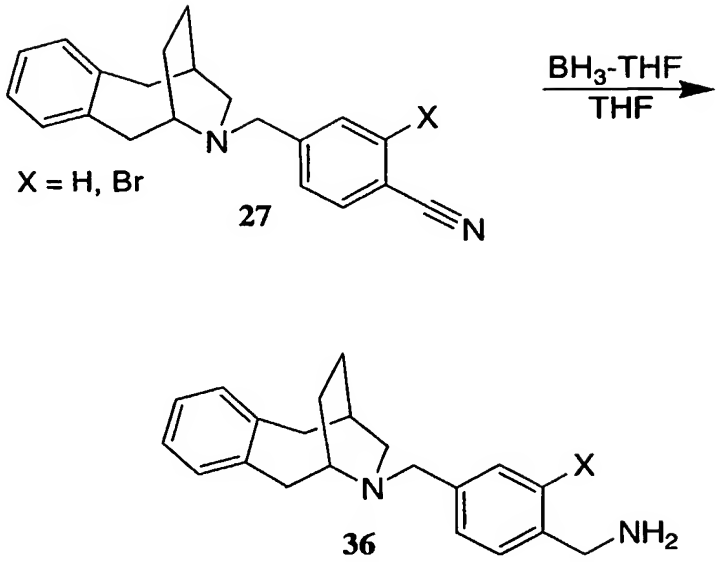

X = H, Br
26
Na(OAc)3BH, AcOH
DCE, room temperature
5
27
DIBAL
DCM
28
NaBH4
MeOH
29

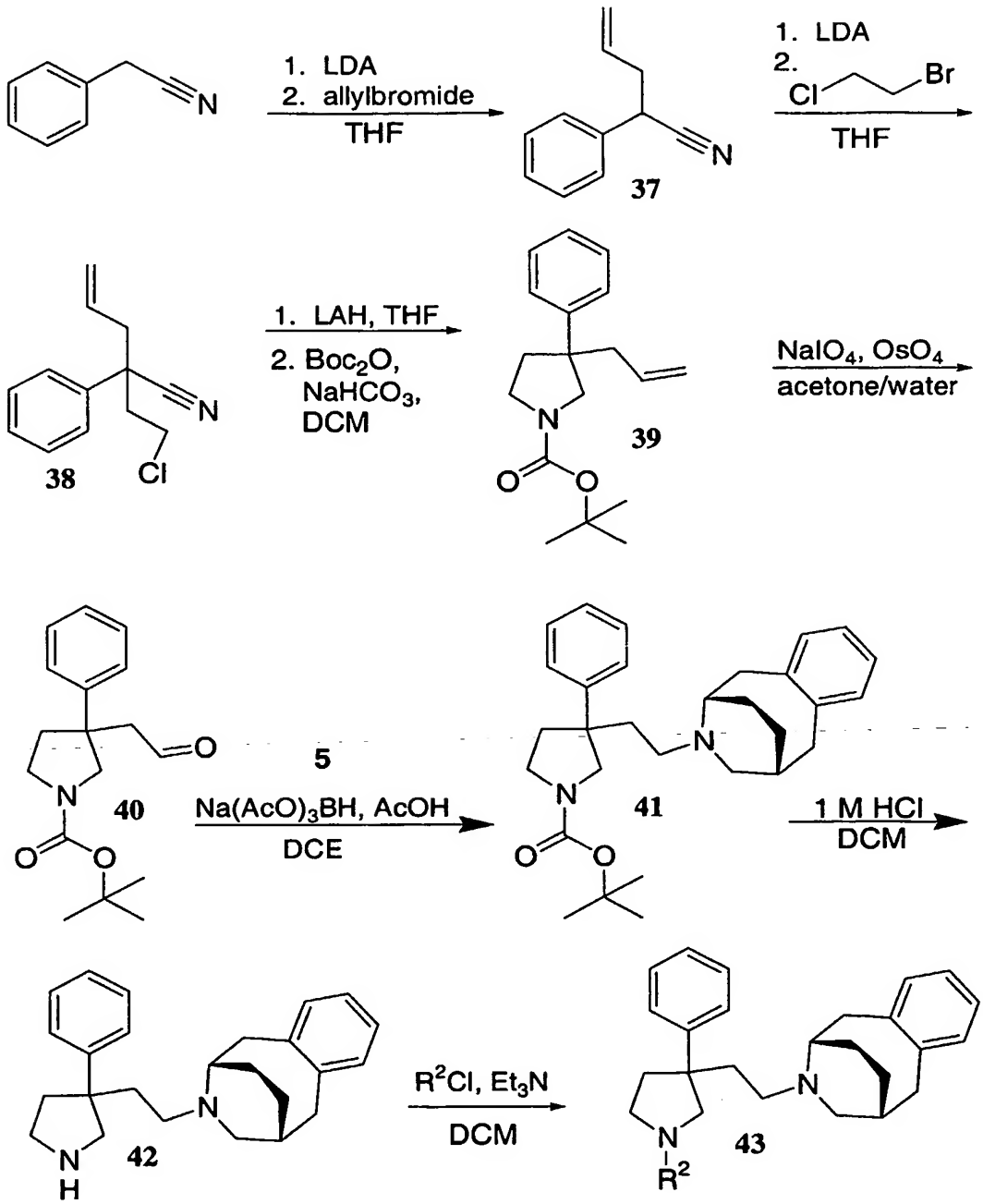
SCHEME 8


HNO3
NH2OH-HCl
pyridine/EtOH,
reflux
TsCl
pyridine, room temperature
BH3·THF
reflux
RCHO
Na(OAc)3BH, AcOH
DCE, room temperature
Zn, AcOH
EtOH, 40°C
1
3
30a
31
31a
32
32a
33
33a
34
34a
35
35a

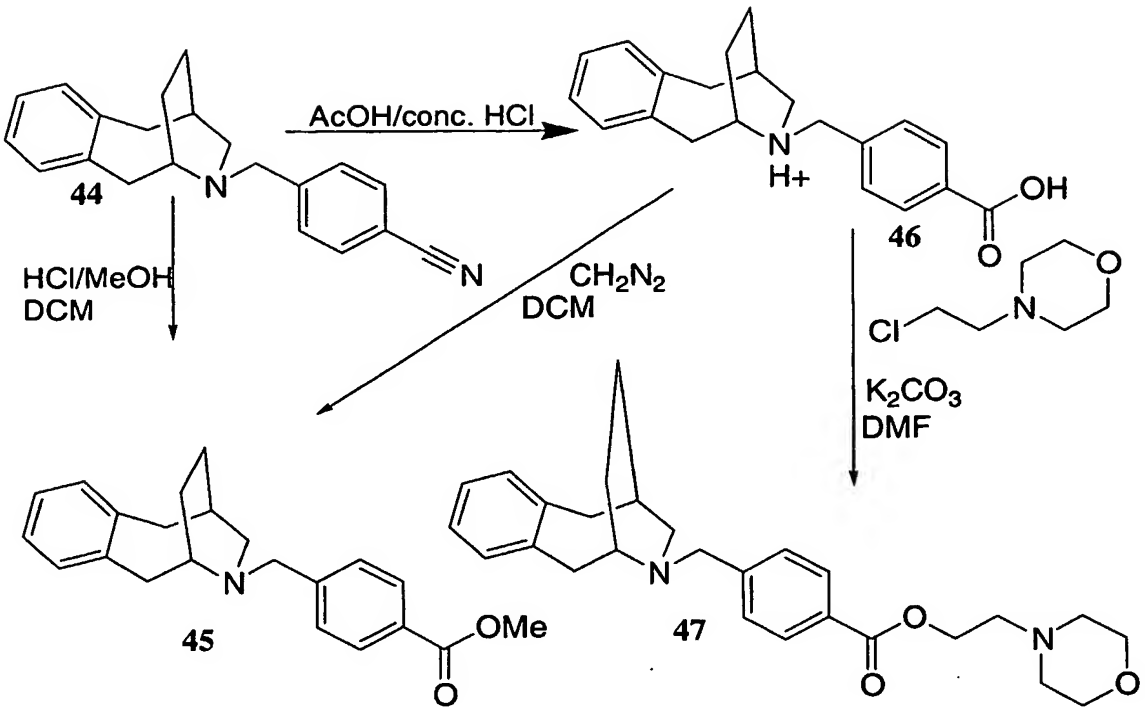
SCHEME 9



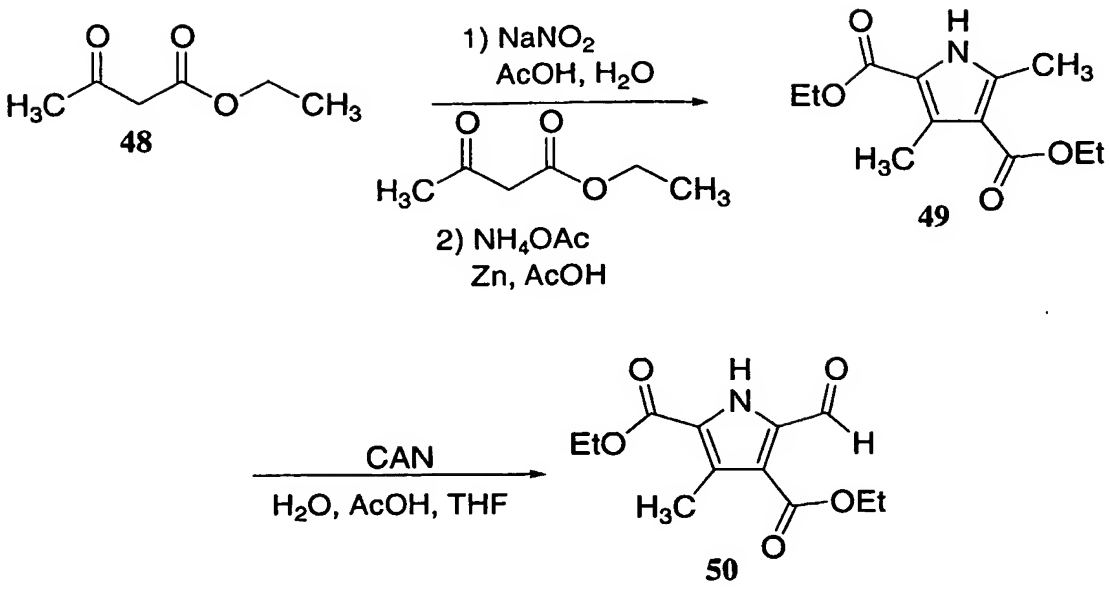
SCHEME 10


1. LDA
2. allylbromide
THF
37
1. LDA
2.
Cl
Br
THF
38
Cl
1. LAH, THF
2. Boc2O, NaHCO3, DCM
39
NaIO4, OsO4
acetone/water
40
5
Na(AcO)3BH, AcOH
DCE
41
1 M HCl
DCM
42
R2Cl, Et3N
DCM
43
R2

SCHEME 11

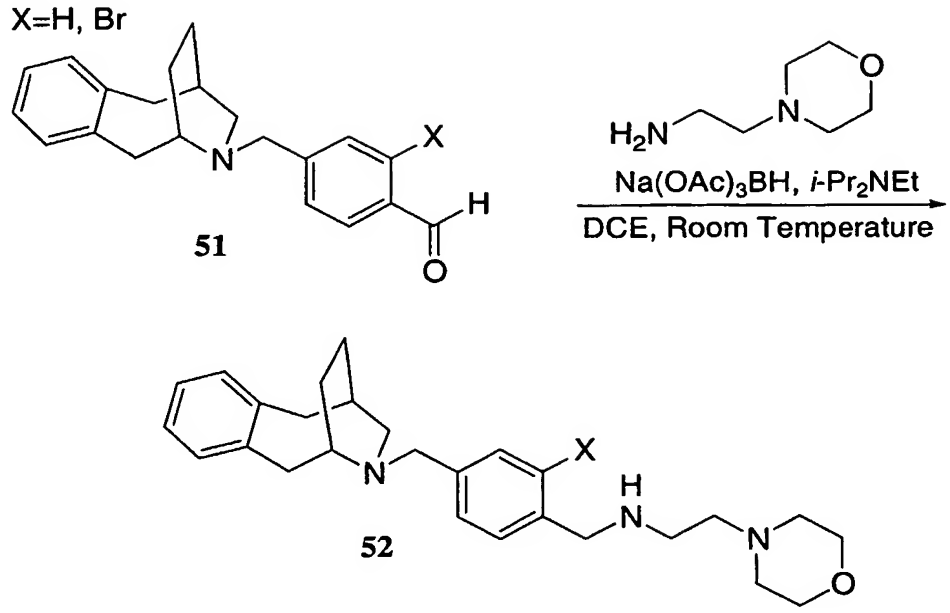

AcOH/conc. HCl
44
N
N
H+
OH
O
46
HCl/MeOH
DCM
CH2N2
DCM
Cl
O
N
K2CO3
DMF
45
OMe
O
47
O
O
N
O

SCHEME 12

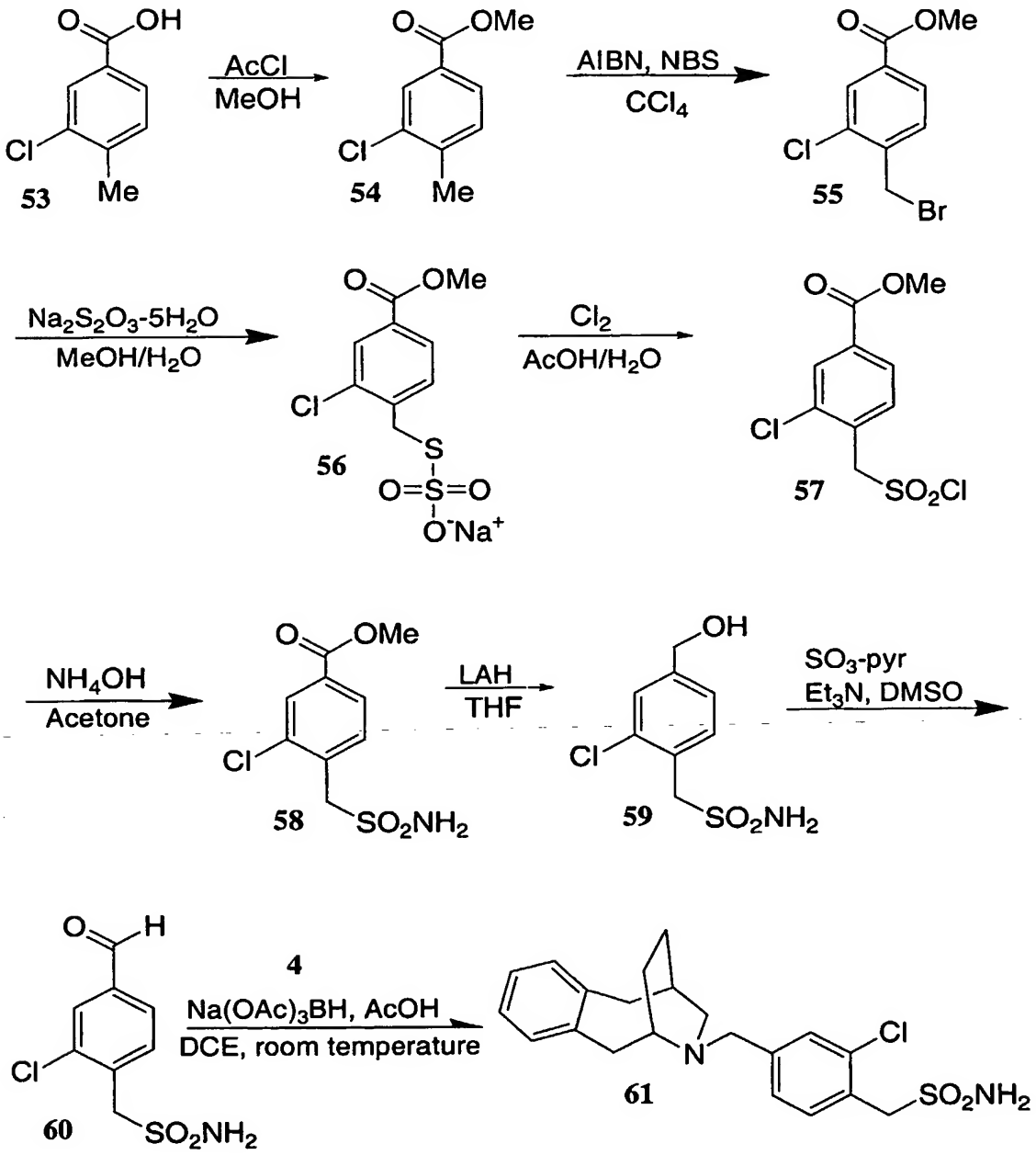


48 49 50

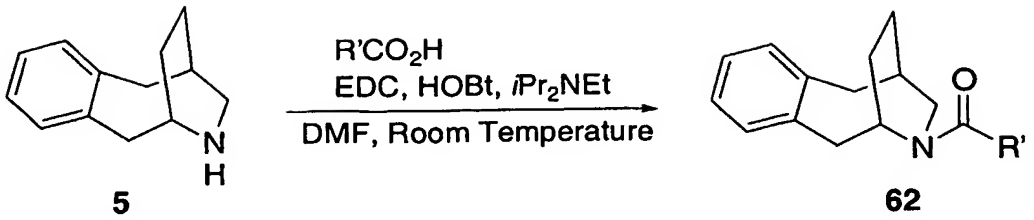
SCHEME 13


X=H, Br
X
H
O
N
51
H2N
N
O
Na(OAc)3BH, i-Pr2NEt
DCE, Room Temperature
X
H
N
N
N
O
52

SCHEME 14


AcCl
MeOH
AIBN, NBS
CCl_4
$Na_2S_2O_3$-5H_2O
MeOH/H_2O
Cl_2
AcOH/H_2O
NH_4OH
Acetone
LAH
THF
SO_3-pyr
Et_3N, DMSO
4
Na(OAc)$_3$BH, AcOH
DCE, room temperature
53
54
55
56
57
58
59
60
61

SCHEME 15



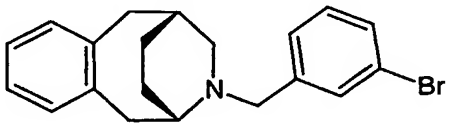
5 62

EXAMPLES

Examples provided are intended to assist in a further understanding of the invention. Particular materials employed, species and conditions are intended to be further illustrative of the invention and not limiting of the reasonable scope thereof.

EXAMPLE 1

(6*S*,9*R*)-12-(3-bromobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo [*a*][8]annulene



Step A: 5,6,7,8,9,10-Hexahydro-6,9-methanobenzo[*a*][8]annulen-11-one

A 3-necked 1 liter flask equipped with an internal thermometer, condenser, and a dropping funnel was charged with a solution of 99.5 g of dibromo-*o*-xylene (0.377 mol) and 131 mL of di-*iso*-propylethylamine (0.753 mol) in 400 mL of CH_3CN under N_2 prior to the dropwise addition of 51.7 g of 1-cyclopent-1-en-1-ylpyrrolidine (0.377 mol) over 45 minutes. The temperature of the reaction reached a maximum of 40-45°C. The resultant mixture was heated to reflux for 4 hours, cooled over night to ambient temperature, then filtered to afford 50.0 g of a light brown solid. The solid was redissolved in 200 mL of CH_3CN and 100 mL of H_2O and heated to reflux overnight. The reaction was cooled to ambient temperature and concentrated *in vacuo* to remove the CH_3CN. The resultant aqueous residue was extracted with Et_2O

(3 x 250 mL). The combined organics were washed with 10% aqueous HCl (2 x 100 mL), filtered through Na_2SO_4, and concentrated *in vacuo* to afford the ketone.

Step B: 5,6,7,8,9,10-Hexahydro-6,9-methanobenzo[*a*][8]annulen-11-one oxime

To a solution of 34.3 g of 5,6,7,8,9,10-hexahydro-6,9-methano-benzo [*a*][8]annulen-11-one (0.184 mol) in 100 mL of pyridine and 100 mL of EtOH was added 29.7 g of hydroxylamine hydrochloride (0.460 mol). The resultant solution was refluxed for 4 hours prior to concentration *in vacuo*. The residue was partitioned between CH_2Cl_2 and 10% aqueous citric acid. The aqueous layer was extracted with CH_2Cl_2 (4x 200 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford the oxime.

Step C: ± 5,6,7,8,9,10-Hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulen-11-one

To a solution of 37.0g of 5,6,7,8,9,10-hexahydro-6,9-methanobenzo [*a*][8]annulen-11-one oxime (0.184 mol) in 500 mL of pyridine under N_2 was added 45.6 g of tosyl chloride (0.239 mol). The resultant solution was stirred at ambient temperature for 2.5 days prior to concentration *in vacuo*. The residue was taken up in $CHCl_3$ (400 mL) washed with 3 N aqueous HCl (1 x 100 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The product was purified by normal phase chromatography (1-7.5% MeOH/CH_2Cl_2) to afford the lactam.

Step D: (*6S,9R*)-5,6,7,8,9,10-Hexahydro-6,9(epiminomethano)benzo[*a*][8] annulene

A 3-necked 1 liter flask equipped with a reflux condenser and dropping funnel was charged with 500 mL of THF, followed by the addition of LAH (20.9 g, 0.551 mol). To this solution was added a dropwise solution of 27.7 g of lactam (0.138 mol) in 300 mL of THF over 45 minutes, maintaining the temperature of the reaction less than 40°C. The mixture was refluxed for 2.5 hours prior to the dropwise addition of 100 mL of a saturated aqueous NH_4Cl solution, followed by 250 mL of a saturated aqueous solution of $NaHCO_3$. The mixture was stirred overnight prior to filtration. The insoluble material was washed with THF. The solution was concentrated *in vacuo*. The amine could be purified in one of two following ways. The unpurified amine could be triturated with hexanes to afford the racemic product. Alternatively, the amine could be purified by chiral HPLC (Chiralpak AD, 240 mL/min, 98-90%

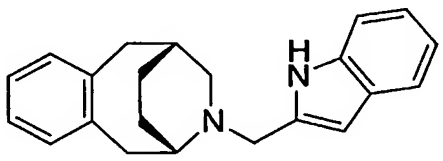
hexanes with diethyl amine/1-5% MeOH/1-5%EtOH) to afford the enantiomerically pure amine products.

Step E: (6*S*,9*R*)-12-(3-bromobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene

To a solution of the 0.050 g of the (6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene (0.27 mmol) in 2 mL of DCE was added 0.0374 mL of 3-bromobenzaldehyde (0.32 mmol), 0.23 mL of di-*iso*-propylethylamine (1.34 mmol), and 0.170g $Na(OAc)BH_3$ (0.80 mmol). The resultant mixture was stirred at ambient temperature under N_2 overnight. The reaction was quenched by the addition of 1 mL of MeOH, stirred for 1 hour, and concentrated *in vacuo*. The residue was dissolved in CH_3CN, filtered through a 0.45 uM needle filter, and purified by reverse phase chromatography to afford the product. This product could be free-based (saturated bicarb/CH_2Cl_2). Proton NMR for the product was consistent with the title compound. ^1H NMR (500 MHz, CD_3OD, HCl salt) δ7.84 (s, 1 H); 7.69 (broad d, J = 7.6 Hz, 1 H); 7.60 (broad d, J = 7.6 Hz, 1 H); 7.45 (broad app t, J = 7.8 Hz, 1 H); 7.16-7.29 (m, 4 H); 4.47 (broad s, 2 H); 3.94 (m, 1 H); 3.61 (broad s, 1 H); 3.49 (m, 1 H); 3.20 (m, 2 H); 3.09 (m, 2 H); 2.71 (m, 1 H); 1.79 (m, 1 H); 1.66 (m, 1 H); 1.55 (m, 1 H); 1.22 (m, 1 H). HRMS (ES) exact mass calculated for $C_{20}H_{22}BrN$ ($M+H^+$): 356.1009. Found 356.1021.

EXAMPLE 2

(6*S*,9*R*)-12-(1*H*-indol-2-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene

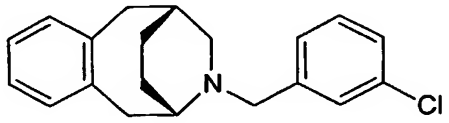


Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 1H-indole-2-carboxaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. ^1H NMR (500 MHz, CD_3OD, HCl salt, 2:1 ratio of salt conformers) δ 7.59 (d, J = 8.0 Hz, 1 H); 7.44 (app t, J = 7.2 Hz, 1 H); 7.17-7.25 (m, 6 H); 6.79 (s, 1 H); 4.63 (m, 2

H); 4.16 (m, 0.33 H); 3.99 (m, 0.67 H); 3.65- 3.75 (m, 2 H); 3.46 (dd, J = 4.1, 14.6 Hz, 0.67 H); 3.39 (dd, J = 3.4, 12.7 Hz, 0.33 H); 3.19- 3.33 (m, 1 H); 3.07-3.15 (m, 2 H); 2.68-2.78 (m, 1 H); 1.90 (m, 0.33 H), 1.81 (m, 0.67 H); 1.69 (m, 0.67 H); 1.47-1.62 (m, 1.33 H); 1.16-1.25 (m, 1 H). HRMS (ES) exact mass calculated for $C_{22}H_{24}N_2$ ($M+H^+$): 317.2012. Found 317.1987.

EXAMPLE 3

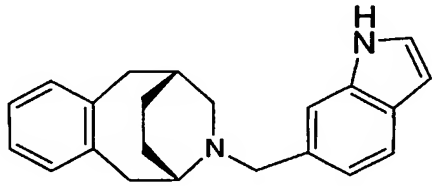
(6*S*,9*R*)-12-(3-chlorobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo [*a*][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 3-chlorobenzaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound.HRMS (ES) exact mass calculated for $C_{20}H_{22}NCl$ ($M+H^+$): 312.1514. Found 312.1530.

EXAMPLE 4

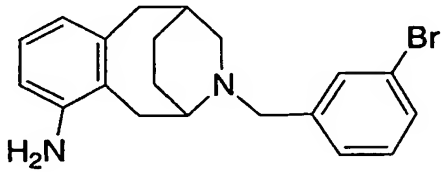
(6S,9R)-12-(1H-indol-6-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[a][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 1H-indole-6-carbaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{22}H_{24}N_2$ ($M+H^+$): 317.2012. Found 317.1987.

EXAMPLE 5

12-(3-bromobenzyl)-5,6,7,8,9,10-hexahydro-6,9(epiminomethano)benzo[*a*][8] annulen-4-amine



Step A: 1,2-bis(hydroxymethyl)-3-nitrobenzene

To 3-nitrophthalic acid (5 g, 23.68 mmol) under N_2 was added 145 mL of BH_3-THF (1M, 142.09 mmol, 142.09 ml). Initial gas evolution was rapid and exothermic. The white mixture was stirred at ambient temperature overnight and then at 50°C for total of 96 hours. The reaction was cooled to 0°C, and quenched by the dropwise addition of pH 7 buffer (230 mL), then by addition of 150mL MeOH and 150mL H_2O_2 (30% aq.). The mixture was extracted with CH_2Cl_2 (3x) and the combined organic layers were dried over Na_2SO_4, filtered, concentrated *in vacuo*. The product was purified by normal phase HPLC (0.25-8%MeOH/CH_2Cl_2) to give the desired product.

Step B: 1,2-bis(bromomethyl)-3-nitrobenzene

To a solution of 1,2-bis(hydroxymethyl)-3-nitrobenzene in AcOH (90 ml) at ambient temperature in a 500 mL flask equipped with a cap was added HBr solution (30% in AcOH, 162 ml). The resultant yellow/brown solution was shielded from light and stirred at ambient temperature for 5 hours. The reaction was concentrated *in vacuo* to afford a brown oil.

Step C: (11E)-1-nitro-5,6,7,8,9,10-hexahydro-6,9-methanobenzo[a][8]annulen-11-one oxime

To a solution of 1,2-bis(bromomethyl)-3-nitrobenzene (2.7 g, 8.74 mmol) in CH_3CN (8 ml) at ambient temperature under N_2 with diethyl *iso*-propylamine (17.48 mmol) was added dropwise 1-cyclopent-1-en-1-ylpyrrolidine (8.74 mmol, 1.27 ml). The reaction was stirred at ambient temperature for 4 days and then at 50 for 6 hours. The mixture was cooled to ambient temperature and

hydroxylamine hydrochloride (43.69 mmol) was added and stirred at ambient temperature for 2 days. The crude reaction was purified by reverse phase HPLC without workup to give a brown oil.

Step D: 1-nitro-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo [a][8] annulen-11-one and 4-nitro-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulen-11-one

To a solution of (11E)-1-nitro-5,6,7,8,9,10-hexahydro-6,9-methanobenzo[a][8]annulen-11-one oxime (810 mg, 3.39 mmol) in pyridine (15 ml) was added 4-methylbenzenesulfonyl chloride (4.28 mmol) at ambient temperature under N_2. The reaction was stirred overnight. The reaction was concentrated *in vacuo*, then partitioned between 10% citric acid and $CHCl_3$. The aqueous layer was extracted with $CHCl_3$ (5 x) and the combined organic solutions were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The product was purified by normal phase HPLC (0.25-7% $MeOH/CH_2Cl_2$) to give a mixture of regioisomers.

Step E: 4-nitro-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8] annulene and 4-nitro-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[a][8]annulene

To a solution of 1-nitro-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[a][8]annulen-11-one and 4-nitro-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[a][8]annulen-11-one (586 mg, 2.38 mmol) in THF (20 ml) was added a solution of BH_3-THF (1M, 7.14 mmol, 7.14 ml) under N_2 at ambient temperature. The reaction was heated to 65°C for 5 hours. The reaction was cooled to ambient temperature and concentrated *in vacuo*. The residue was taken up in 1 mL of 4:1 MeOH/conc. HCl and heated to reflux for 3 hours. The mixture was cooled to ambient temperature, poured into aqueous Na_2CO_3 and extracted with EtOAc (5 x). The combined organic solutions were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The product was purified by normal phase HPLC (1-15%$MeOH(10\%NH_4OH)/CH_2Cl_2$) to give a mixture of diastereomers.

Step F: 12-(3-bromobenzyl)-4-nitro-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene chloride

A solution of 1-nitro-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[a][8]annulene and 4-nitro-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo

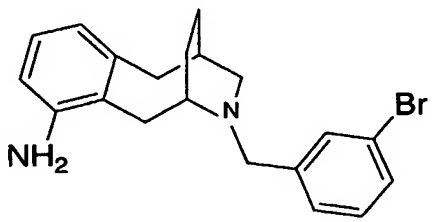
[a][8]annulene (365 mg, 1.57 mmol) in 10 ml of DCE was treated with 4-bromo-benzaldehyde (1.89 mmol), $Na(OAc)_3BH$ (4.71 mmol), and Acetic acid (7.85 mmol). The reaction stirred overnight at ambient temperature. The mixture was quenched by the addition of aqueous satd. $NaHCO_3$, stirred for 30 minutes, and then extracted with EtOAc (3 x). The combined organic solutions were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The product was purified on by normal phase HPLC (5-50% EtOAc/Hexanes) to give the desired as well as the undesired regioisomer (12-(3-bromobenzyl)-1-nitro-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8] annulene chloride). Proton NMR for the product was consistent with the title compound. ESI+ MS: 401 [M] and 403 [M+2].

Step G: 12-(3-bromobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulen-4-amine

Zn dust was added to a suspension of 12-(3-bromobenzyl)-4-nitro-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene (89 mg, 0.222 mmol) in EtOH/HOAc (4:1, 5 mL). The reaction was heated to 40°C and stirred vigorously for 2 hours. The mixture was quenched by the addition of satd. aqueous Na_2CO_3. The aqueous solution was extracted with EtOAc (3x) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The product was purified by normal phase HPLC (0.25-10%MeOH(10%NH_4OH)/ CH_2Cl_2) to give a yellow oil. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{20}H_{24}BrN_2$ ($M+H^+$): 371.1117. Found 371.1118.

EXAMPLE 6

(6S,9R)- 12-(3-bromobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulen-4-amine



Step A: 2,3-Dibromo-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo [*a*][8]annulene

To a solution of 5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo [*a*][8]annulene (3.59 g, 19.2 mmol) in 150 mL CH_2Cl_2 and 22 mL H_2SO_4 was added NBS (5.12 g, 28.75 mmol). The resultant mixture was heated to 45°C for 18 hours at which time the reaction was quenched by the slow addition of ammonium hydroxide until cessation of gas evolution and alkalinization was achieved. The mixture was partitioned between cold water and CH_2Cl_2, the layers separated, and the aqueous layer extracted with CH_2Cl_2 (1X). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford a residue determined by LC/MS and NMR to contain a 2.5:1 ratio of the desired dibromide to a tribromide compound.

Step B: 2,3-Dibromo-4-nitro-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene

To a solution of the dibromide and tribromide mixture (5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene and a tribromide contaminant) (<4.62 g, <16.4 mmol) in 20 mL of CCl4 at –45°C was added neat nitric acid (20 mL) and an additional 10 mL of CCl4 as a rinse. The resultant yellow solution was stirred for 30 minutes at –40°C before an additional 20 mL of nitric acid was added and the reaction warmed to –20°C for 30 minutes. The reaction was poured into 500 mL of ice cold water prior to the slow addition of solid Na_2CO_3 until cessation of gas evolution. The resultant mixture was extracted with CH_2Cl_2 (3x), the combined organic layers dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford a mixture of nitrated products by LC/MS and NMR.

Step C: 5,6,7,8,9,10-Hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulen-4-amine

To a solution of the mixture of nitrated products (containing 2,3-dibromo-4-nitro-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene) (<4.80 g, <14.67 mmol) in 100 mL EtOH and 50 mL EtOAc was added 2.4 g of 10% Pd/C followed by the dropwise addition of hydrazine (2.76 mL, 88.0 mmol). The reaction was then heated to 85°C. After 1 hour, an additional portion of palladium (1.2 g) and hydrazine (1.5 mL) was added and the reaction refluxed for an additional 1.5 hours. After the reaction was cooled and concentrated, the resultant dibromide

salt of the title compound was obtained as well as two other products as determined by LC/MS and NMR.

Step D: *Tert*-butyl 4-amino-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene-12-carboxylate

To a clear solution of a mixture of 5,6,7,8,9,10-Hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulen-4-amine dibromide salt and two other regioisomers of the aniline group (4.44g, 12.2 mmol) in 300 mL of CH_2Cl_2 was added Et_3N (5.10 mL, 36.6 mmol). The solution was cooled to 0°C prior to the addition of di-*tert*-butyl dicarbonate (2.80 mL, 12.2 mmol) and 4-dimethylaminopyridine (1.49 g, 12.2 mmol). The reaction was stirred at 0°C for 2 hours before it was partitioned between CH_2Cl_2, and a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted 2x CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by normal phase chromatography (10-50% EtOAc/hexanes, 40 mm long, 80 ml/min) to afford three major products. The clean fraction containing the desired product by NMR and LC/MS were combined.

Step E: *Tert*-butyl 4-[(trifluoroacetyl)amino]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene-12-carboxylate

To a solution of the *tert*-butyl 4-amino-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene-12-carboxylate (0.741 g, 2.45 mmol) in 10 mL of CH_2Cl_2 was added pyridine (0.99 mL, 12.25 mmol) and trifluoroacetic anhydride (1.04 mL, 7.35 mmol). The resultant solution was stirred overnight at ambient temperature under N2. The reaction was partitioned between saturated aqueous solution of $NaHCO_3$ and CH_2Cl_2. The aqueous layer was extracted with additional CH_2Cl_2 (2x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified on by normal phase chromatography (10-50% EtOAc/hexanes, 80 ml/min) to afford clean product by NMR and LC/MS.

Step F: 4-[(Trifluoroacetyl)amino]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene chloride

HCl (g) was bubbled through a solution of *tert*-butyl 4-[(trifluoroacetyl)amino]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo

[a][8]annulene-12-carboxylate (0.824 g, 2.07 mmol) in 20 mL of CH_2Cl_2 at 0°C. After 1 hour, the solution was allowed to warm to ambient temperature, then was concentrated *in vacuo*.

Step G: N-[12-(3-Bromobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[a][8]annulen-4-yl]-2,2,2-trifluoroacetamide

To a solution of 4-[(trifluoroacetyl)amino]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene chloride (0.565g 1.68 mmol) in 20 ml DCE at ambient temperature under N_2 was added 3-bromobenzaldehyde (0.29 mL, 2.52 mmol), Et_3N (0.47 mL, 3.36 mmol), sodium triacetoxyborohydride (1.07 g, 5.03 mmol), and acetic acid (0.58 mL, 10.1 mmol). The resultant solution was stirred overnight. The reaction was filtered over 3x1g SCX columns prior to purification by normal phase chromatography (1-5%MeOH (5% NH_4OH)/CH_2Cl_2, 50 ml/min). NMR and LC/MS were consistent with the product obtained.

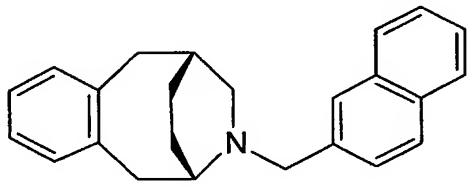
Step H: (6S,9R)- 12-(3-bromobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulen-4-amine

To a solution of the N-[12-(3-bromobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulen-4-yl]-2,2,2-trifluoroacetamide (0.780 g, 1.67 mmol) in 60 mL of MeOH was added water (3.6 mL) and K_2CO_3 (1.20 g, 8.68 mmol). The resultant solution was stirred overnight at ambient temperature. The reaction was then heated to 65°C for 4 hours, prior to the addition of additional K_2CO_3 (1.6 g) and 10 mL H_2O. After an additional 2 hours, a second addition of 1g of K_2CO_3 was added. The reaction was heated for 2.5 days at 65°C prior concentration *in vacuo*. The residue was partitioned between H_2O and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 (2x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The product was purified first by normal phase chromatography (0.25-10% MeOH(10%NH_4OH)/CH_2Cl_2, 80 ml/min) the by reverse phase chromatography. All product containing fractions were free-based (bicarb and CH_2Cl_2 extraction) to afford the title compound. Proton NMR for the product was consistent with the title compound. ^1H NMR (500 MHz, $CDCl_3$) δ 7.38 (s, 1 H); 7.33 (broad d, J = 7.8 Hz, 1 H); 7.16 (broad d, J = 7.5 Hz, 1 H); 7.12 (t, J = 7.8 Hz, 1 H); 6.93 (t, J = 7.7 Hz, 1 H); 6.57 (broad t, J = 8.5), 2 H); 3.67 (d, J = 13.9 Hz, 1 H); 3.55 (d, J = 13.9 Hz, 1 H); 3.46 (broad s, 1 H); 3.26 (m, 1 H); 3.04 (dd,

J = 5.1, 14.7 Hz, 1 H); 2.77-2.85 (m, 4 H); 2.69 (dd, J = 8.1, 15.3 Hz, 1 H); 2.44 (m, 1 H); 1.80 (m, 1 H); 1.63 (m, 1 H); 1.38 (m, 1 H); 1.28 (m, 1 H).
HRMS (ES) exact mass calculated for $C_{20}H_{24}BrN_2$ ($M+H^+$): 371.1117. Found 371.1118.

EXAMPLE 7

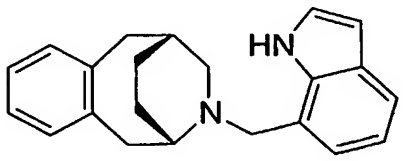
(6*S*,9*R*)-12-(2-naphthylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 2-naphthaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound.
HRMS (ES) exact mass calculated for $C_{24}H_{25}N$ ($M+H^+$): 328.2060. Found 328.2070.

EXAMPLE 8

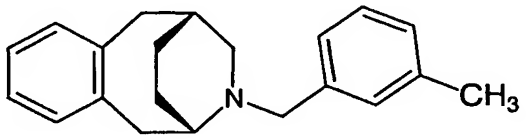
(6*S*,9*R*)-12-(1H-indol-7-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[a][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 1H-indole-7-carbaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound.
HRMS (ES) exact mass calculated for $C_{22}H_{24}N_2$ ($M+H^+$): 317.2012. Found 317.1983.

EXAMPLE 9

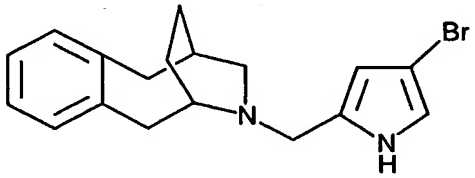
(6*S*,9*R*)-12-(3-methylbenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo [*a*][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 3-methylbenzaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{21}H_{25}N$ ($M+H^+$): 292.2060. Found 292.2082.

EXAMPLE 10

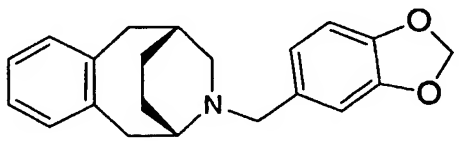
(6*S*,9*R*)-12-[(4-bromo-1*H*-pyrrol-2-yl)methyl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 4-bromo-1H-pyrrole-2-carbaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. ^{1}H NMR (500 MHz, CD_3OD, TFA salt) δ 7.14-7.25 (m, 4 H); 6.93 (d, J = 1.5 Hz, 1 H); 6.46 (d, J = 1.5 Hz, 1 H); 4.40 (s, 2 H); 4.00 (broad s, 1 H); 3.56 (broad d, J = 12.2 Hz, 1 H); 3.18-3.34 (m, 3 H); 3.11 (dd, J = 10.0, 15.6 Hz, 1 H); 3.02 (app d, J = 15.4 Hz, 1 H); 2.71 (broad s, 1 H); 1.78 (m, 1 H); 1.41-1.77 (m, 1 H); 1.22-1.31 (m, 1 H). HRMS (ES) exact mass calculated for $C_{18}H_{22}BrN_2$ ($M+H^+$): 345.0961. Found 345.0976.

EXAMPLE 11

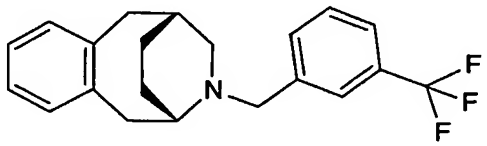
(6*S*,9*R*)-12-(1,3-benzodioxol-5-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 1,3-benzodioxole-5-carbaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. ^{1}H NMR (500 MHz, CD_3OD, 2:1 ratio of salt conformers) δ 7.19-7.26 (m, 3 H); 7.06-7.17 (m, 3 H); 6.94 (dd, J = 3.7, 17.8 Hz, 1 H); 6.04 (s, 2 H); 4.33-4.38 (m, 2 H); 4.04 (m, 0.33 H); 3.92 (m, 0.67 H); 3.90-3.94 (m, 1.34 H); 3.43-3.51 (m, 1.33 H), 3.04-3.25 (m, 3.33 H); 2.64-2.78 (m, 1 H); 1.98 (m, 0.33 H); 1.45-1.79 (m, 2.67 H); 1.20 (m, 1 H). HRMS (ES) exact mass calculated for $C_{21}H_{23}NO_2$ ($M+H^+$): 322.1802. Found 322.1800.

EXAMPLE 12

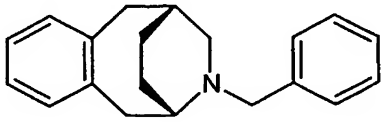
(6*S*,9*R*)-12-[3-(trifluoromethyl)benzyl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 3-(trifluoromethyl)benzaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{21}H_{22}F_3N$ ($M+H^+$): 346.1777. Found 346.1798.

EXAMPLE 13

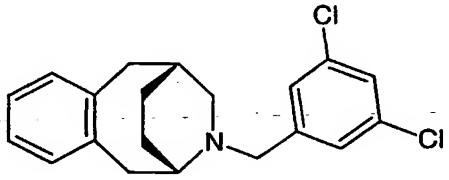
(6*S*,9*R*)-12-benzyl-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with benzaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{20}H_{23}N$ ($M+H^+$): 278.1903. Found 278.1908.

EXAMPLE 14

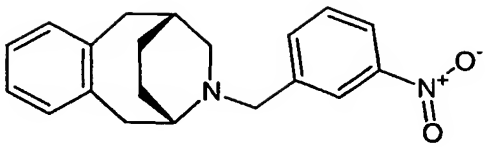
(6*S*,9*R*)-12-(3,5-dichlorobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 3,5-dichlorobenzaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{20}H_{21}Cl_2N$ ($M+H^+$): 346.1124. Found 346.1143.

EXAMPLE 15

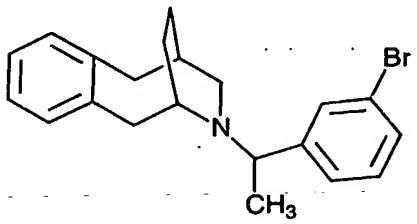
(6*S*,9*R*)-12-(3-nitrobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo [*a*][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 3-nitrobenzaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{20}H_{22}N_2O_2$ ($M+H^+$): 323.1754. Found 323.1768.

EXAMPLE 16

(6*S*,9*R*)-12-[1-(3-bromophenyl)ethyl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene

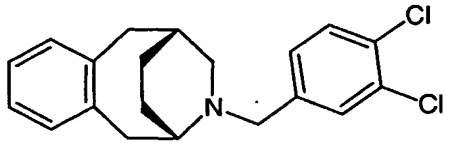


Following the procedures described in Example 1, (*6S,9R*)-5,6,7,8,9,10-Hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene was prepared (Steps A-D). To this amine (0.10 g, 0.53 mmol) under N_2 were added 3'-bromo-acetophenone (0.07 mL, 0.53 mmol) and titanium tetra-*iso*-propoxide (0.20 mL, 0.67 mmol). The neat reactants were stirred for 1.5 hours at ambient temperature prior to dilution with 1 mL of EtOH and treatment with sodium cyanoborohydride (0.0225 g, 0.36 mmol). The resultant slurry was stirred for 20 hours at ambient temperature, then quenched by the addition of water. The resultant inorganic precipitate was washed with EtOH. The filtrate was concentrated *in vacuo* and the residue partitioned in water and EtOAc. The aqueous layer was washed with EtOAc (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The product was purified by normal phase chromatography (30% CH_2Cl_2/(0.25-5% MeOH/Hexanes, 35 ml/min) to afford two products: the title compound and its diastereomer. Proton NMR for the product was consistent with the title compound.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (s, 1 H); 7.25 (dt, J = 1.0, 8.1 Hz, 1 H); 7.25 (m, 1 H); 7.16 (t, J = 7.8 Hz, 1 H); 7.10 (m, 2 H); 7.04 (dd, J = 1.7, 6.6 Hz, 1 H); 6.97 (app d, J = 6.6 Hz, 1 H); 3.73 (q, J = 6.6 Hz, 1 H); 3.29 (m, 1 H); 3.17 (dd, J = 4.2, 14.1 Hz, 1 H); 2.97 (dd, J = 4.9, 10.3 Hz, 1 H); 2.95 (dd, J = 3.4, 13.9, 1 H); 2.89 (dd, J = 9.3, 14.4 Hz, 1 H); 2.76 (app d, J = 10.2 Hz, 1 H); 2.62 (dd, J = 7., 14.8 Hz, 1 H); 2.50 (m, 1 H); 1.72 (m, 1 H); 1.62 (m, 1 H); 1.30 (d, J = 6.6 Hz, 3 H); 1.18 (m, 1 H); 1.05 (m, 1 H). HRMS (ES) exact mass calculated for $C_{21}H_{24}BrN$ ($M+H^+$): 370.1165. Found 370.1165.

EXAMPLE 17

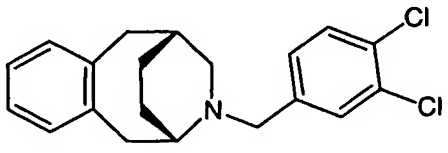
(6*S*,9*R*)-12-(3,4-dichlorobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo [*a*][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 3,4-dichlorobenzaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{20}H_{21}Cl_2N$ ($M+H^+$): 346.1124. Found 346.1145.

EXAMPLE 18

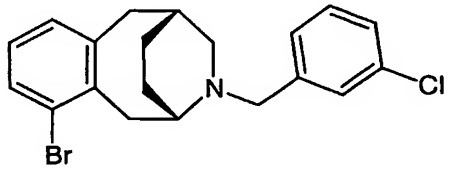
(6*S*,9*R*)-12-(3-fluorobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo [*a*][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 3-fluorobenzaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{20}H_{22}FN$ ($M+H^+$): 296.1809. Found 296.1830.

EXAMPLE 19

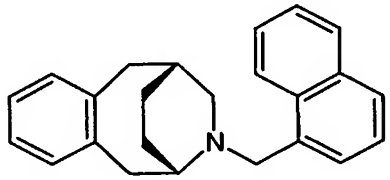
(6*S*,9*R*)-4-bromo-12-(3-chlorobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 3-chlorobenzaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. ^1H NMR (500 MHz, $CDCl_3$) δ 744 (dd, J = 1.5, 7.8 Hz, 1 H); 7.16 (app d, J = 5.2 Hz, 2 H); 7.06 (app s, 1 H); 6.96-7.01 (m, 3 H); 3.64 (d, J = 13.9 Hz, 1 H); 3.53 (d, J = 13.7 Hz, 1 H); 3.33 (m, 1 H); 3.23 (dd, J = 5.6, 14.4 Hz, 1 H); 3.09-3.16 (m, 3 H); 2.87 (dd, J = 6.7, 14.8 Hz, 1 H); 2.69 (app d, J = 3.9 Hz, 2 H); 2.47 (m, 1 H); 1.85 (m, 1 H); 1.73 (m, 1 H); 1.37 (m, 2 H). ESI+ MS: 390.1 [M] and 392.1 [M+2].

EXAMPLE 20

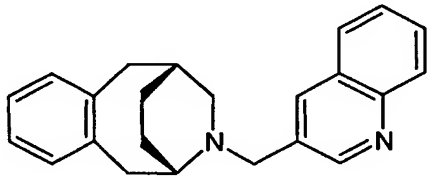
(6*S*,9*R*)-12-(1-naphthylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo [*a*][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 1-naphthaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{24}H_{25}N$ ($M+H^+$): 328.2060. Found 328.2070.

EXAMPLE 21

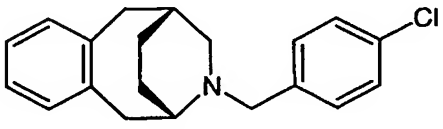
(6*S*,9*R*)-12-(quinolin-3-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo [*a*][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with quinoline-3-carbaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{23}H_{24}N_2$ ($M+H^+$): 329.2012. Found 329.2000.

EXAMPLE 22

(6*S*,9*R*)-12-(4-chlorobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo [*a*][8]annulene

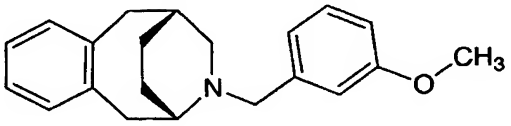


Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 4-chlorobenzaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound.

HRMS (ES) exact mass calculated for $C_{20}H_{22}NCl$ ($M+H^+$): 312.1514. Found 312.1531.

EXAMPLE 23

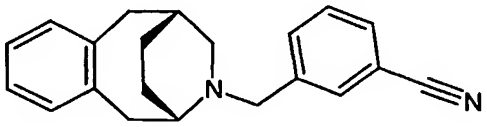
(6*S*,9*R*)-12-(3-methoxybenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 3-methoxybenzaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{21}H_{25}NO$ ($M+H^+$): 308.2009. Found 308.2023.

EXAMPLE 24

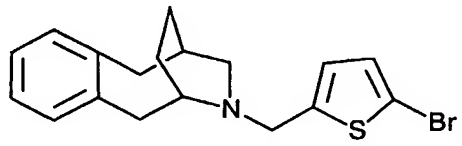
3-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulen-12-ylmethyl]benzonitrile



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 3-formylbenzonitrile, the title compound was obtained. Proton NMR for the product was consistent with the title compound. ESI+ MS: 303 [M+1]. HRMS (ES) exact mass calculated for $C_{21}H_{22}N_2$ ($M+H^+$): 303.1856. Found 303.1870.

EXAMPLE 25

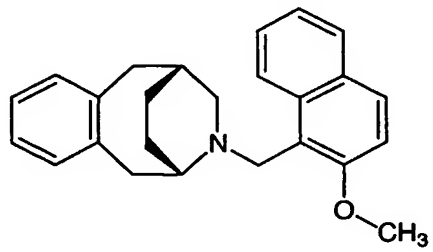
(6*S*,9*R*)-12-[(5-bromothien-2-yl)methyl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 5-bromothiophene-2-carbaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{18}H_{20}BrNS$ ($M+H^+$): 362.0573. Found 362.0538.

EXAMPLE 26

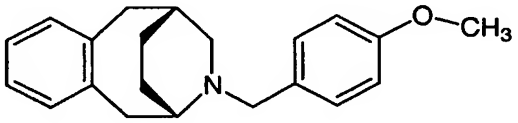
(6*S*,9*R*)-12-[(2-methoxy-1-naphthyl)methyl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 2-methoxy-1-naphthaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{25}H_{27}NO$ ($M+H^+$): 358.2166. Found 358.2146.

EXAMPLE 27

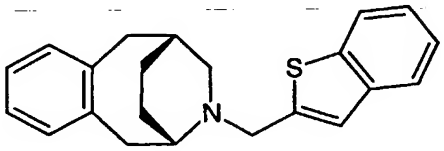
(6*S*,9*R*)-12-(4-methoxybenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo [*a*][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 4-methoxybenzaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{21}H_{25}NO$ ($M+H^+$): 308.2009. Found 308.2020.

EXAMPLE 28

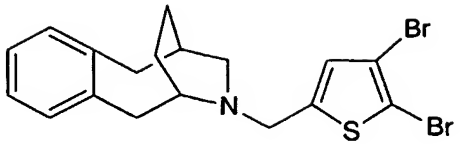
(6*S*,9*R*)-12-(1-benzothien-2-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 1-benzothiophene-2-carbaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{22}H_{23}NS$ ($M+H^+$): 334.1624. Found 334.1614.

EXAMPLE 29

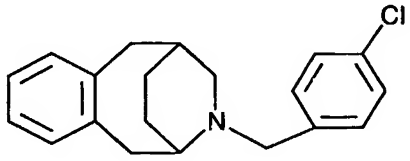
(6*S*,9*R*)-12-[(4,5-dibromothien-2-yl)methyl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 4,5-dibromothiophene-2-carbaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{18}H_{20}Br_2NS$ ($M+H^+$): 439.9678. Found 439.9678.

EXAMPLE 30

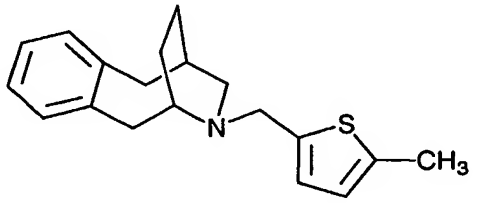
12-(4-chlorobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8] annulene



Following the procedures (Steps A-D) described in Example 1, the racemic compound (±) 5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo [*a*][8]annulene was obtained. Replacing 3-bromobenzaldehyde of Step E with 4-chlorobenzaldehyde and (*6S,9R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene with (±) 5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{20}H_{23}ClN$ ($M+H^+$): 312.1514. Found 312.1508.

EXAMPLE 31

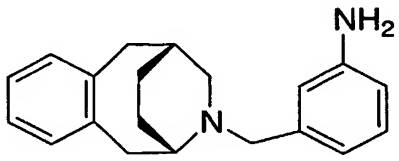
(6*S*,9*R*)-12-[(5-methylthien-2-yl)methyl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 5-methylthiophene-2-carbaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{21}H_{25}NO$ ($M+H^+$): 298.1624. Found 298.1634.

EXAMPLE 32

3-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulen-12-ylmethyl]aniline



Step A: (6*S*,9*R*)-12-(3-nitrobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene

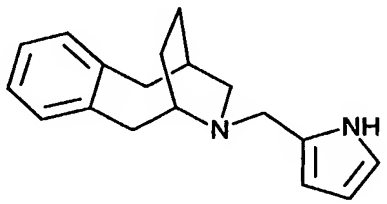
Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 3-nitrobenzaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compund.

Step B: 3-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6epiminomethano)benzo[a][8] annulen-12-ylmethyl]aniline

To a solution of (6*S*,9*R*)-12-(3-nitrobenzyl)-5,6,7,8,9,10-hexahydro 6,9-(epiminomethano)benzo[a][8]annulene (35 mg, 0.109 mmol) in EtOH (2 ml)was added AcOH (500 uL). Zinc dust (2.18 mmol) was added in one portion and heated to 40°C. After 5 hours, the reaction was poured into a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted 2x with EtOAc and washed organic layer with brine 1x. The organic solution was dried over $MgSO_4$ and concentrated. The crude reaction product was purified by reverse phase HPLC. The product was then dissolved in EtOAc, washed 1x with satd $NaHCO_3$, 1x brine, and dried over $MgSO_4$ to give the desired product. ^1H NMR (500 MHz, $CDCl_3$) δ 7.10-7.14 (m, 2 H); 7.05-7.09 (m, 2 H); 7.01-7.03 (m, 1 H); 6.70 (d, J = 7.6 Hz, 1 H); 6.63 (broad s, 1 H); 6.56 (app d, J = 7.8 Hz, 1 H); 3.70 (d, J = 13.2 Hz, 1 H); 6.63 (d, J = 12.7 Hz, 1 H); 3.62 (broad s, 1 H); 3.31 (broad s, 1 H); 3.19 (dd, J = 4.2, 14.4 Hz, 1 H); 3.13 (app d, J = 14.6 Hz, 1 H); 2.89 (dd, J = 8.9, 14.6 Hz, 1 H); 2.82 (broad s, 1 H); 2.75 (dd, J = 7.9, 14.9 Hz, 1 H); 2.47 (m, 1 H); 1.83 (m, 1 H); 1.59 (m, 1 H); 1.22-1.32 (m, 2 H). HRMS (ES) exact mass calculated for $C_{20}H_{24}N_2$ ($M+H^+$): 293.2012. Found: 293.2012.

EXAMPLE 33

(6*S*,9*R*)-12-(1*H*-pyrrol-2-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene

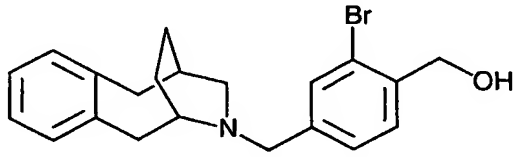


Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 1H-pyrrole-2-carbaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. ^1H NMR (500 MHz, CD_3OD, TFA salt, 60:40 ratio of salt conformers) δ 10.71 (broad s, 0.4 H); 10.65 (broad s, 0.6 H); 7.17-7.25 (m, 3 H); 7.12-7.16 (m, 2 H); 6.90 (app s, 1 H); 6.42 (app s, 1 H); 6.20 (app s, 1 H); 4.36-4.47 (m 2 H); 4.08 (m, 0.4 H); 3.91 (m, 0.6 H); 3.64 (dd, J = 11.1, 13.9 Hz, 0.6 H); 3.56 (app d, J = 13.0 Hz, 0.6 H); 3.38 (dd, J = 4.1, 15.4 Hz, 0.6 H); 3.29-3.34 (m, 0.8 H); 2.98-3.25 (m, 3.4 H); 2.66-2.75

(m, 1 H); 1.72-1.80 (m, 1 H); 1.62-1.69 (m, 0.6 H); 1.43-1.58 (m, 1.4 H); 1.09-1.23 (m, 1 H). HRMS (ES) exact mass calculated for $C_{18}H_{23}N_2$ ($M+H^+$): 267.1856. Found 267.1857.

EXAMPLE 34

{2-bromo-4-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8] annulen-12-ylmethyl]phenyl}methanol



Step A: 2-bromo-4-(dibromomethyl)benzonitrile

To solution of 2-bromo-4-methylbenzonitrile (285 mg, 1.454 mmol) in CCl_4 (15 ml) was added NBS (2.91 mmol, 518 mg) followed by AIBN (0.07 mmol, 12 mg). The mixture was refluxed under N_2 for 20 hours. The reaction was concentrated *in vacuo* and the residue was partitioned between EtOAc and satd $NaHCO_3$. The organic layer was washed with water, brine, then dried over Na_2SO_4. The solution was filtered and concentrated *in vacuo* to afford a mixture of bis to mono Br by NMR.

Step B: 2-bromo-4-formylbenzonitrile

The 2-bromo-4-(dibromomethyl)benzonitrile mixture was dissolved in 15 mL EtOH (95%). $AgNO_3$ was added and the mixture was heated to reflux for 1 hour. The salts were filtered through celite and the filtrate was concentrated *in vacuo*. The crude product was purified by normal phase HPLC (5-50% EtOAc/ Hexane) to give the desired product.

Step C: 2-bromo-4-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[a][8]annulen-12-ylmethyl]benzonitrile

Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step A with 2-bromo-4-formylbenzonitrile, the title compound was obtained. Proton NMR for the product was consistent with the title compound.

ESI+ MS: 381 [M] and 383 [M+2].

Step D: 2-bromo-4-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[a][8]annulen-12-ylmethyl]benzaldehyde

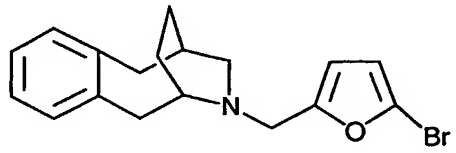
Diisobutylaluminum hydride (1 M, 0.25 mmol, 250 ul) was added to a solution of 2-bromo-4-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo [a][8]annulen-12-ylmethyl]benzonitrile (64 mg, 168 mmol) in 1.5 ml of dry CH_2Cl_2 at –78°C. The reaction was stirred from –78°C to ambient temperature overnight. LC/MS analysis shows mostly conversion to the imine. The reaction was cooled to 0°C and treated with H_2O, Rochelle's salt, and EtOAc. The solution was poured into a separatory funnel and separated. The organic phase was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude imine was dissolved in CH_2Cl_2 and treated with a catalytic amount of silica gel and a small amount of water. The mixture stirred at ambient temperature for 2 hours and was then filtered and concentrated *in vacuo*. The crude product was purified by normal phase HPLC to give the desired product.

Step E: 2-bromo-4-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[a][8]annulen-12-ylmethyl]phenyl}methanol

A solution of 2-bromo-4-[5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulen-12-ylmethyl]benzaldehyde (18 mg, 0.057 mmol) in 1 ml of MeOH was cooled to –78°C and was treated $NaBH_4$ (0.11 mmol, 4.3 mg). The reaction stirred at –78°C for 1 hour, then 1 ml of H_2O was added and the reaction warmed up to ambient temperature. The mixture was extracted with CH_2Cl_2. The organic solution was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by reverse phase HPLC to give the desired product. The compound was freebased (saturated bicarbonate/CH_2Cl_2). Proton NMR for the product was consistent with the title compound. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (s, 1 H); 7.37 (d, J = 7.8 Hz, 1 H); 7.21 (d, J = 7.6 Hz, 1 H); 7.13 (m, 2 H); 7.02-7.06 (m, 2 H); 4.73 (s, 2 H); 3.73 (d, J = 13.7 Hz, 1 H); 3.62 (d, J = 13.7 Hz, 1 H); 3.18 (dd, J = 4.6, 14.4 Hz, 1 H); 3.08 (dd, J = 3.9, 14.6 Hz, 1 H); 2.88 (dd, J = 8.8, 14.4 Hz, 1 H); 2.72-2.80 (m, 3 H); 2.47 (m, 1 H); 1.82 (m, 1 H); 1.57 (m, 1 H); 1.33 (m, 1 H); 1.19-1.26 (m, 1 H). HRMS (ES) exact mass calculated for $C_{21}H_{25}BrNO$ ($M+H^+$): 386.1114. Found 386.1104.

EXAMPLE 35

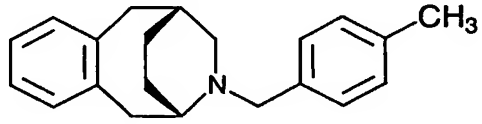
(6*S*,9*R*)-12-[(5-bromo-2-furyl)methyl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 5-bromo-2-furaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{18}H_{21}BrNO$ ($M+H^+$): 346.0801. Found 346.0808.

EXAMPLE 36

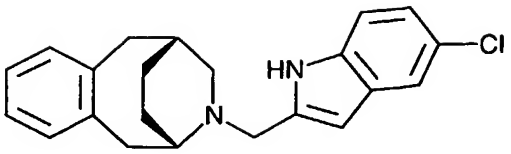
(6*S*,9*R*)-12-(4-methylbenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo [*a*][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 4-methylbenzaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{21}H_{25}N$ ($M+H^+$): 292.2060. Found 292.2072.

EXAMPLE 37

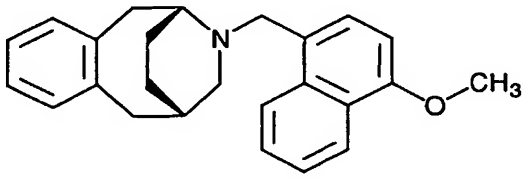
(6*S*,9*R*)-12-[(5-chloro-1*H*-indol-2-yl)methyl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 5-chloro-1H-indole-2-carbaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{22}H_{23}N_2Cl$ ($M+H^+$): 351.1623. Found 361.1617.

EXAMPLE 38

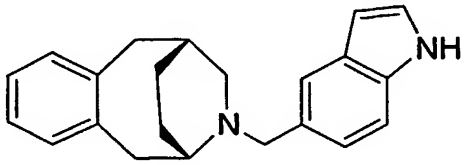
(6*R*,9*S*)-12-[(4-methoxy-1-naphthyl)methyl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 4-methoxy-1-naphthaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. ESI+ MS: 358 [M+1]. HRMS (ES) exact mass calculated for $C_{25}H_{27}NO$ ($M+H^+$): 358.2166. Found 358.2153.

EXAMPLE 39

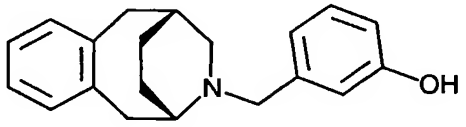
(6*S*,9*R*)-12-(1H-indol-5-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[a][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 1H-indole-5-carbaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{22}H_{24}N_2$ ($M+H^+$): 317.2012. Found 317.1990.

EXAMPLE 40

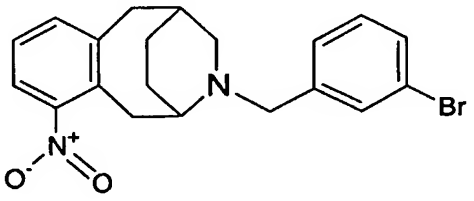
3-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulen-12-ylmethyl]phenol



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 3-hydroxybenzaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{20}H_{23}NO$ ($M+H^+$): 294.1853. Found 294.1879.

EXAMPLE 41

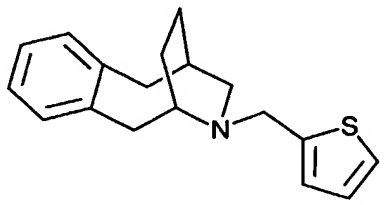
12-(3-bromobenzyl)-4-nitro-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo [*a*][8]annulene



Following the procedures described in Example 5 (Steps A-F), the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{20}H_{21}BrN_2O_2$ ($M+H^+$): 401.0859. Found 401.0829.

EXAMPLE 42

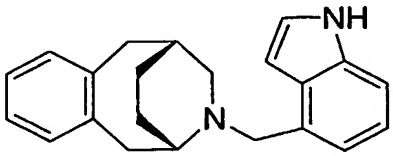
(6*S*,9*R*)-12-(thien-2-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo [*a*][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with thiophene-2-carbaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{18}H_{22}N_2S$ ($M+H^+$): 284.1467. Found 284.1475.

EXAMPLE 43

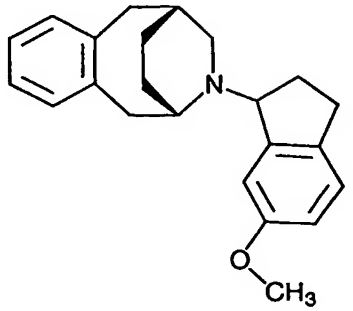
(6*S*,9*R*)-12-(1H-indol-4-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[a][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 1H-indole-4-carbaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{22}H_{24}N_2$ ($M+H^+$): 317.2012. Found 317.1984

EXAMPLE 44

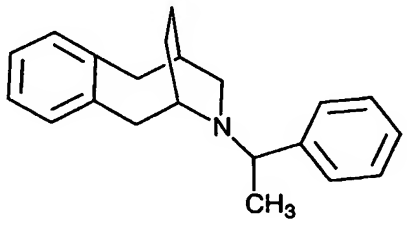
(6*S*,9*R*)-12-[(1*R*)-6-methoxy-2,3-dihydro-1H-inden-1-yl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene and (6*S*,9*R*)-12-[(1*S*)-6-methoxy-2,3-dihydro-1H-inden-1-yl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene



Following the procedures described in Example 16, replacing 3'-bromoacetophenone with 6-methoxyindan-1-one, the title compound diastereomers were obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{23}H_{27}NO$ ($M+H^+$): 334.2166. Found 334.2192.

EXAMPLE 45

(6*S*,9*R*)-12-[(1*R*)-1-phenylethyl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene and (6*S*,9*R*)-12-[(1*S*)-1-phenylethyl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene

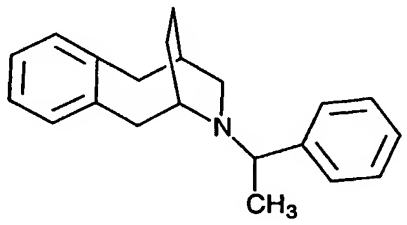


Following the procedures described in Example 16, replacing 3'-bromoacetophenone with acetophenone, the title compound diastereomers were obtained. Proton NMR for the product was consistent with the title compound.

HRMS (ES) exact mass calculated for $C_{21}H_{26}N$ ($M+H^+$): 292.2060. Found 292.2060.

EXAMPLE 46

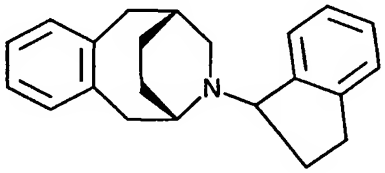
(6*S*,9*R*)-12-[(1*R*)-1-phenylethyl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo [a][8]annulene or (6*S*,9*R*)-12-[(1*S*)-1-phenylethyl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene



Following the procedures described in Example 45, a mixture of diastereomers was obtained. These were separated (DeltaPak C-18, 30-100% MeOH/0.05% NH_4Cl-HCl (aq)) to afford the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{21}H_{26}N$ ($M+H^+$): 292.2060. Found 292.2066.

EXAMPLE 47

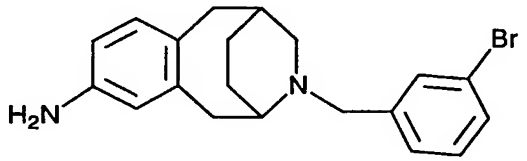
(6*S*,9*R*)-12-[(1*R*)-2,3-dihydro-1H-inden-1-yl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene and (6*S*,9*R*)-12-[(1*S*)-2,3-dihydro-1H-inden-1-yl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene



Following the procedures described in Example 16, replacing 3'-bromoacetophenonewith indan-1-one, the title compound diastereomers were obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{22}H_{25}N$ ($M+H^+$): 304.2060. Found 304.2079.

EXAMPLE 48

12-(3-bromobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8] annulen-3-amine



Step A: (11Z)-2-nitro-5,6,7,8,9,10-hexahydro-6,9-methanobenzo[a][8]annulen-11-one oxime

A suspension of the known compound 2-nitro-5,6,7,8,9,10-hexahydro-6,9-methanobenzo[a][8]annulen-11-one (4.8 g, 20.75 mmol), hydroxylamine (3.61 g, 51.89 mmol), and pyridine/EtOH (20 mL/20 mL) was heated to reflux for 4 hours. The reaction was then cooled to ambient temperature and concentrated *in vacuo*. The mixture was partitioned between 10% citric acid and CH_2Cl_2. The aqueous layer was separated and washed with CH_2Cl_2 (3 x). The combined organic solutions were dried over Na_2SO_4, concentrated, and purified by normal phase chromatography (50% Et_2O/pet. ether-60%) to give one isomer (less polar), mixed isomers, and the other isomer (more polar).

Step B: 3-nitro-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8] annulen-11-one

Dissolve (11Z)-2-nitro-5,6,7,8,9,10-hexahydro-6,9-methanobenzo[a] [8]annulen-11-one oxime (1.37 g, 5.56 mmol) in pyridine (40ml). Add tosyl chloride (1.38 g, 7.22 mmol) and stir at ambient temperature overnight. The reaction was concentrated *in vacuo*, treated with 3 N HCl and a minimal amount of CH_2Cl_2 and allowed to stir at ambient temperature for 4 hours. The mixture was extracted with $CHCl_3$ (4 x) and the combined organic solutions were dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by normal phase HPLC (70% EtOAc/hexanes - 100% EtOAc) to give a pale yellow solid.

Step C: 3-nitro-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8] annulene

Add BH_3 soln (1M, 0.69 mmol, 690 ul) to a soln of 3-nitro-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulen-11-one (57 mg, 0.231 mmol) in THF (3ml) and heat to reflux for 23 hours. Remove stir bar (rinse with MeOH) and concentrate. Take up in 4 mL MeOH and 1 ml of conc HCl and heat to reflux for 1.5 hours. The mixture was cooled to ambient temperature and poured into aq Na_2CO_3. The aqueous solution was extracted with EtOAc (5x) and CH_2Cl_2 (3x). The combined organic solutions were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The reaction was purified by normal phase chromatography (0-5-10-15% MeOH(NH_3/CH_2Cl_2) to give a yellow oil.

Step D: 12-(3-bromobenzyl)-3-nitro-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene chloride

Following the procedures described in Example 1, replacing 5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene of Step E with 3-nitro-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{20}H_{21}BrN_2O_2$ ($M+H^+$): 401.0859. Found 401.0855.

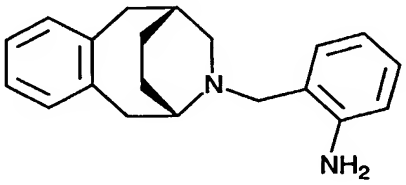
Step E: 12-(3-bromobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulen-3-amine

Zinc dust (163 mg, 2.50 mmol) was added to a suspension of 12-(3-bromobenzyl)-3-nitro-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8] annulene chloride (50 mg, 0.125 mmol) in EtOH/HOAc (4:1, 2.5 mL) and heat to 40°C with vigorous stirring for 1 hour. The reaction was poured into sat Na_2CO_3 and extracted with EtOAc (2x). The combined organic solutions were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by reverse phase chromatography to give a clear oil. The product was freebased (saturated bicarbonate/CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$) δ 7.44 (s, 1 H); 7.34 (d, J = 7.8 Hz, 1 H); 7.22 (7.6 Hz, 1 H); 7.15 (t, J = 7.7 Hz, 1 H); 6.83 (d, J = 7.8 Hz, 1 H); 6.48 (dd, J = 2.1, 7.8 Hz, 1 H); 6.42 (app d, 2.0 Hz, 1 H); 3.72 (d, J = 13.7 Hz, 1 H); 3.62 (d, J = 13.9 Hz, 1 H); 3.20 (m, 1 H); 3.06 (dd, J = 4.6, 14.6 Hz, 1 H); 3.01 (dd, J = 3.7, 14.6 Hz, 1 H); 2.79 (dd, J = 9.0, 14.9 Hz, 1 H); 2.77 (app d, J = 3.6 Hz, 1

H); 2.61 (dd, J = 7.8, 14.6 Hz, 1 H); 2.40 (m, 1 H); 1.79 (m, 1 H); 1.54 (m, 1 H); 1.30 (m, 1 H).
HRMS (ES) exact mass calculated for $C_{20}H_{23}BrN_2$ ($M+H^+$): 371.1118. Found 371.1118.

EXAMPLE 49

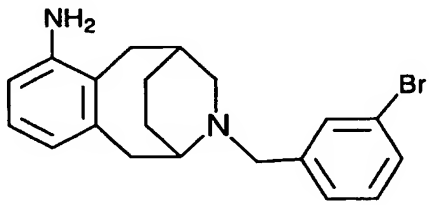
2-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulen-12-ylmethyl]phenylamine



Following the procedures described in Example 32 (Steps A and B), replacing 3-nitrobenzaldehyde of Step A with 2-nitrobenzaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. ^1H NMR (500 MHz, $CDCl_3$) δ 7.0-7.13 (m, 2 H); 7.03-7.07 (m, 2 H); 6.98-7.01 (m, 2 H); 6.64 (app t, J = 7.5 Hz, 1 H); 6.55 (d, J = 7.5 Hz, 1 H); 4.31 (broad s, 2 H); 3.62 (s, 2 H); 3.24 (m, 1 H); 3.06 (dd, J = 5.5, 14.5 Hz, 1 H); 3.02 (dd, J = 5.5, 14.5 Hz, 1 H); 2.85 *dd, J = 7.00, 15.0 Hz, 1 H); 2.71-2.76 (m, 2 H); 2.58 (dd, J = 4.5, 10.5 Hz, 1 H); 2.47 (m, 1 H); 1.87 (m 1 H); 1.69 (m, 1 H); 1.39 (m, 2 H).
HRMS (ES) exact mass calculated for $C_{20}H_{26}Cl_2N_2$ ($M+H^+$): 293.2012. Found 293.2014

EXAMPLE 50

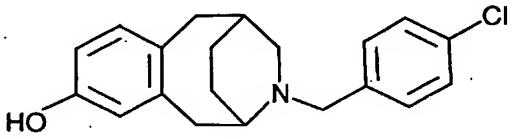
12-(3-bromobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulen-1-amine



Following the procedures described in Example 5 (Steps A-G), isolating the minor diastereomer, 12-(3-bromobenzyl)-1-nitro-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene chloride, in Step F and replacing 12-(3-bromobenzyl)-4-nitro-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene chloride of Step G with 12-(3-bromobenzyl)-1-nitro-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene chloride, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{20}H_{23}BrN_2$ ($M+H^+$): 371.1117. Found 371.1117.

EXAMPLE 51

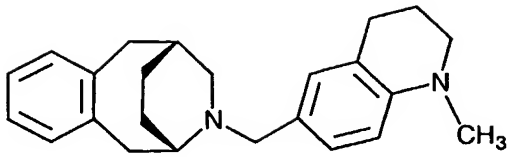
12-(4-chlorobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8] annulen-3-ol



Following the procedures described in references by Belanger, *et al.*, (1982, *J. Org. Chem.* 47:4-329 and 1983, *Can. J. Chem.* 61:2177) 2-hydroxy-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene chloride was obtained. Following the procedures described in Example 1, replacing 5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene of Step E with 3-hydroxy-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene and 3-bromobenzaldehyde with 4-chlorobenzaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. TLC (15% MeOH/$CHCl_3$ + NH_3 (g)) R_f= 0.784.

EXAMPLE 52

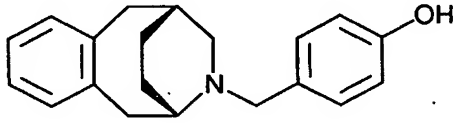
(6*S*,9*R*)-12-[(1-methyl-1,2,3,4-tetrahydroquinolin-6-yl)methyl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 1-methyl-1,2,3,4-tetrahydroquinoline-6-carbaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{24}H_{30}N_2$ ($M+H^+$): 347.2482. Found 347.2448

EXAMPLE 53

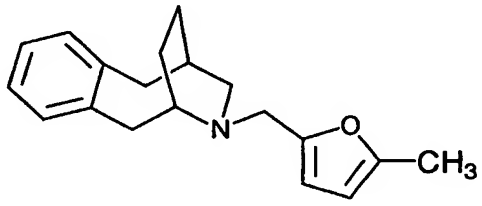
4-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulen-12-ylmethyl]phenol



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 4-(hydroxymethyl)phenol, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{20}H_{23}NO$ ($M+H^+$): 294.1853. Found 294.1861

EXAMPLE 54

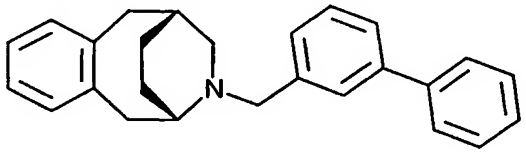
(6*S*,9*R*)-12-[(5-methyl-2-furyl)methyl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 5-methyl-2-furaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{20}H_{23}BrN_2$ ($M+H^+$): 371.1118. Found 371.1118.

EXAMPLE 55

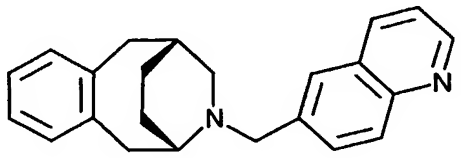
(6*S*,9*R*)-12-(1,1'-biphenyl-3-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 1,1'-biphenyl-3-carbaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{26}H_{27}N$ ($M+H^+$): 354.22163. Found 354.2232.

EXAMPLE 56

(6*S*,9*R*)-12-(quinolin-6-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene

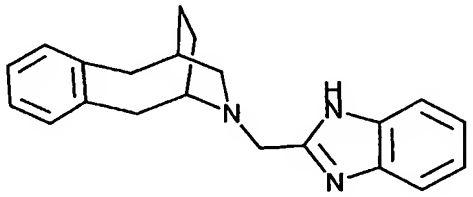


Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with quinoline-6-carbaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound.

HRMS (ES) exact mass calculated for $C_{23}H_{24}N_2$ ($M+H^+$): 329.2012. Found 329.1993

EXAMPLE 57

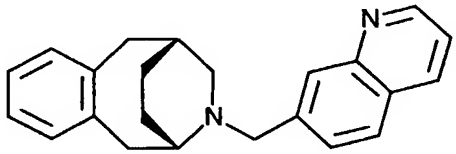
(6*S*,9*R*)-12-(1H-benzimidazol-2-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 1H-benzimidazole-2-carbaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{21}H_{23}N_3$ ($M+H^+$): 318.1965. Found 318.1961.

EXAMPLE 58

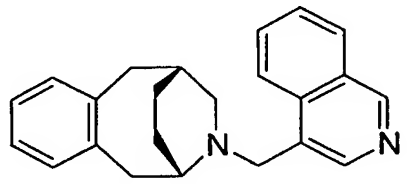
(6*S*,9*R*)-12-(quinolin-7-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 1-quinolin-7-ylmethanimine, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{23}H_{24}N_2$ ($M+H^+$): 329.2012. Found 329.1993

EXAMPLE 59

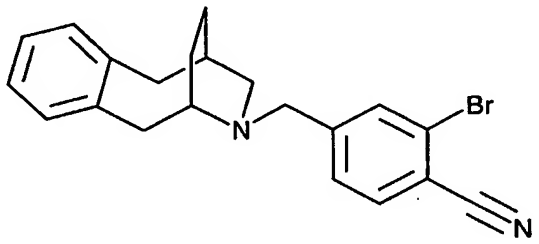
(6*S*,9*R*)-12-(isoquinolin-4-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with isoquinoline-4-carbaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{23}H_{24}N_2$ ($M+H^+$): 329.2012. Found 329.1998

EXAMPLE 60

2-bromo-4-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8] annulen-12-ylmethyl]benzonitrile



Step A: 2-bromo-4-(dibromomethyl)benzonitrile

To solution of 2-bromo-4-methylbenzonitrile (285 mg, 1.454 mmol) in CCl_4 (15 ml) was added NBS (2.91 mmol, 518 mg) followed by AIBN (0.07 mmol, 12 mg). The mixture was refluxed under N_2 for 20 hours. The reaction was concentrated *in vacuo* and the residue was partitioned between EtOAc and satd $NaHCO_3$. The organic layer was washed with water, brine, then dried over Na_2SO_4. The solution was filtered and concentrated *in vacuo* to afford a mixture of bis to mono Br by NMR.

Step B: 2-bromo-4-formylbenzonitrile

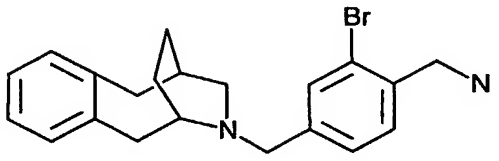
The 2-bromo-4-(dibromomethyl)benzonitrile mixture was dissolved in 15 mL EtOH (95%). $AgNO_3$ was added and the mixture was heated to reflux for 1 hour. The salts were filtered through celite and the filtrate was concentrated *in vacuo*. The crude product was purified by normal phase HPLC (5-50% EtOAc/Hexane) to give the desired product.

Step C: 2-bromo-4-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[a][8]annulen-12-ylmethyl]benzonitrile

Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 2-bromo-4-formylbenzonitrile, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{21}H_{21}BrN_2$ ($M+H^+$): 380.0888. Found 380.0875.

EXAMPLE 61

1-{2-bromo-4-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8] annulen-12-ylmethyl]phenyl}methanamine

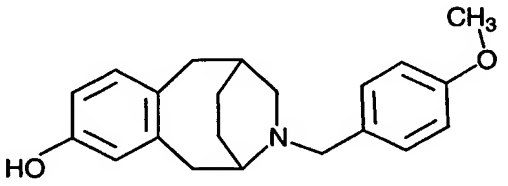


Following the procedures described in Example 61, 2-bromo-4-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8] annulen-12-ylmethyl]benzonitrile was obtained. A solution of 2-bromo-4-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulen-12-ylmethyl] benzonitrile (15 mg, 0.039 mmol) in 1 ml of dry THF was cooled to 0°C under N_2. BH_3·THF solution was added (1M, 0.08 mmol, 80 ul) and the reaction stirred from 0°C to ambient temperature for 1 hour. The mixture was then heated to reflux for 5 hours. The reaction was cooled to ambient temperature and concentrated *in vacuo*. The mixture was then treated with 3 ml of MeOH and 1 ml of conc. HCl and heated to reflux for 0.5 hour. The crude product was purified by reverse phase HPLC to give the desired

product. HRMS (ES) exact mass calculated for $C_{21}H_{26}BrN_2$ ($M+H^+$): 385.1274. Found 385.1273.

EXAMPLE 62

12-(4-methoxybenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8] annulen-3-ol

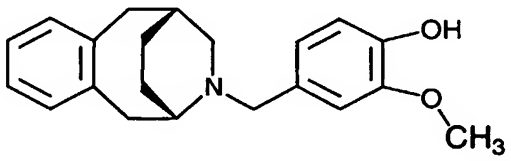


Following the Belanger *et al.* procedures, 2-hydroxy-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene chloride was obtained. Following the procedures described in Example 1, replacing 5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene of Step E with 3-hydroxy-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene and 3-bromobenzaldehyde with 4-methoxybenzaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. Elemental analysis calculated for $C_{21}H_{25}ClNO_2$ * HCl C: 70.08; H: 7.28; N: 3.89; Cl: 9.85

Found: C: 69.84; H: 8.53; N: 3.68; Cl: 9.63

EXAMPLE 63

4-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulen-12-ylmethyl]-2-methoxyphenol

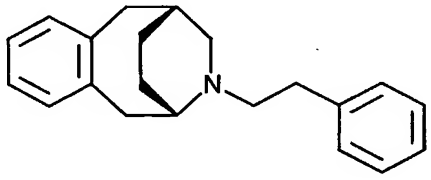


Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 4-hydroxy-3-methoxybenzaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title

compound. HRMS (ES) exact mass calculated for $C_{21}H_{25}NO_2$ ($M+H^+$): 324.1958. Found 324.1956

EXAMPLE 64

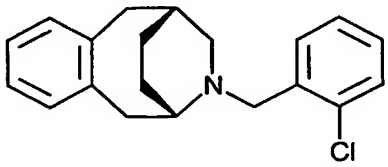
(6*S*,9*R*)-12-(2-phenylethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*] [8] annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with phenylacetaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{21}H_{25}N$ ($M+H^+$): 292.2060. Found 292.2082

EXAMPLE 65

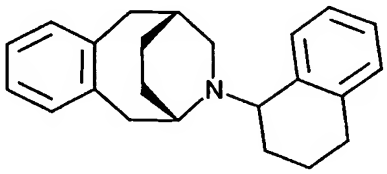
(6*S*,9*R*)-12-(2-chlorobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*] [8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 2-chlorobenzaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{20}H_{22}NCl$ ($M+H^+$): 312.1514. Found 312.1524

EXAMPLE 66

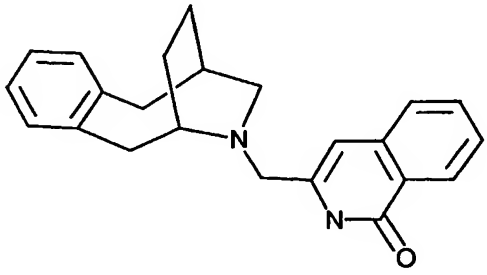
(6*S*,9*R*)-12-[(1*R*)-1,2,3,4-tetrahydronaphthalen-1-yl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene and (6*S*,9*R*)-12-[(1*S*)-1,2,3,4-tetrahydronaphthalen-1-yl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[a][8]annulene



Following the procedures described in Example 16, replacing 3'-bromoacetophenone with 3,4-dihydronaphthalen-1(2H)-one, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{23}H_{27}N$ ($M+H^+$): 318.2216. Found 318.2231.

EXAMPLE 67

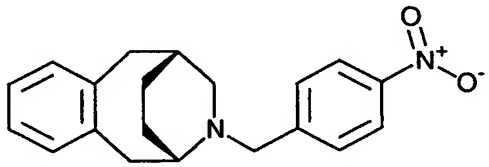
3-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulen-12-ylmethyl]isoquinolin-1(2H)-one



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 1-oxo-1,2-dihydroisoquinoline-3-carbaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{23}H_{24}N_2O$ ($M+H^+$): 345.1962. Found 345.1964.

EXAMPLE 68

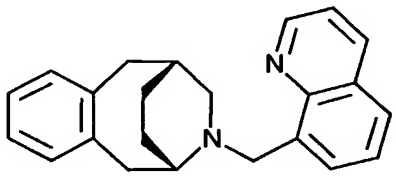
(6*S*,9*R*)-12-(4-nitrobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo [*a*][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 4-nitrobenzaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{20}H_{22}N_2O_2$ ($M+H^+$): 323.1754. Found 323.1757

EXAMPLE 69

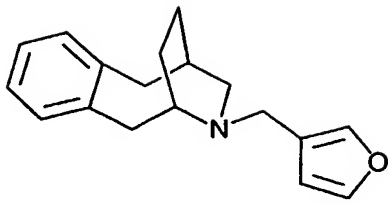
(6*S*,9*R*)-12-(quinolin-8-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with quinoline-8-carbaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{23}H_{24}N_2$ ($M+H^+$): 329.2012. Found 329.1984

EXAMPLE 70

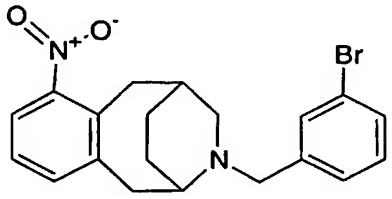
(6*S*,9*R*)-12-(3-furylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo [*a*][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 3-furaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{18}H_{21}NO$ ($M+H^+$): 268.1696. Found 268.1683.

EXAMPLE 71

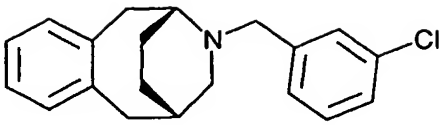
12-(3-bromobenzyl)-1-nitro-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo [*a*][8]annulene



Following the procedures described in Example 5 (Steps A-F), the title compound was obtained as the minor diastereomer, 12-(3-bromobenzyl)-1-nitro-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene chloride. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{20}H_{21}BrN_2O_2$ ($M+H^+$): 401.0859. Found 401.0882.

EXAMPLE 72

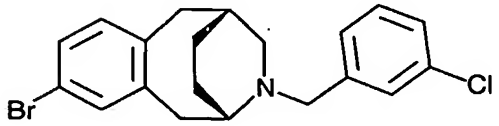
(6*R*,9*S*)-12-(3-chlorobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo [*a*][8]annulene



Following the procedures described in Example 1, replacing (6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene with (6*R*,9*S*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene and 3-bromobenzaldehyde of Step E with 3-chlorobenzaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{20}H_{22}ClN$ ($M+H^+$): 312.1514. Found 312.1527.

EXAMPLE 73

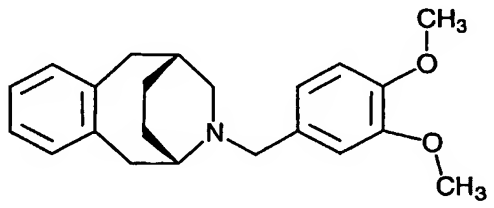
(6*S*,9*R*)-3-bromo-12-(3-chlorobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene



Following the procedures described in Example 06 (Step A), the monobromide (6*S*,9*R*)-3-bromo-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo [a][8]annulene was obtained. Following the procedures described in Example 01, replacing (6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene with (6*S*,9*R*)-3-bromo-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8] annulene and 3-bromobenzaldehyde of Step E with 3-chlorobenzaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{20}H_{21}BrClN$ ($M+H^+$): 390.0619. Found 390.0641.

EXAMPLE 74

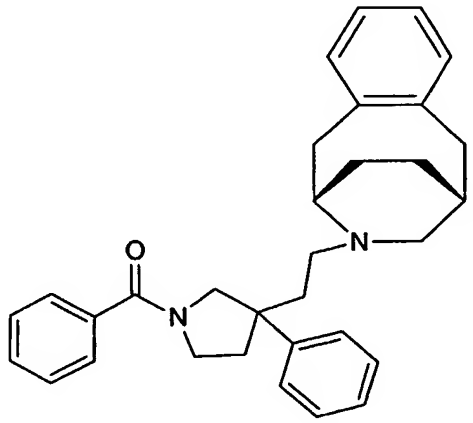
(6*S*,9*R*)-12-(3,4-dimethoxybenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 3,4-dimethoxybenzaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{22}H_{27}NO_2$ ($M+H^+$): 338.2115. Found 338.2098.

EXAMPLE 75

(6*S*,9*R*)-12-{2-[(3*R*)-1-benzoyl-3-phenylpyrrolidin-3-yl]ethyl}-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene and (6*S*,9*R*)-12-{2-[(3*S*)-1-benzoyl-3-phenylpyrrolidin-3-yl]ethyl}-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[a][8]annulene



Step A: 2-phenylpent-4-enenitrile

In a 1L round bottom flask charged with 500mL of THF and N,N-di-*iso*-propylamine (55 mmol, 7.71 ml) at -78°C under nitrogen was added *n*-BuLi (2.5 M, 55 mmol, 22ml) dropwise. The resultant clear colorless solution was stirred 10 minutes at -78°C, before a solution of phenylacetonitrile (5.86 g, 50 mmol) in 20 mL THF was added via cannula (plus 5 mL rinse). The enolate was stirred at -78°C for 15 minutes and at 0°C for 15 minutes, then cooled to -78°C at which time a solution of 3-bromoprop-1-ene (75 mmol, 6.49 ml) in 20 mL THF (plus 5 ml wash) was added dropwise. The reaction stirred -78°C for 10 minutes at which time TLC (10% ethyl acetate/hexanes) showed reaction was complete. The mixture warmed to ambient temperature and was quenched by addition of 300 mL of sat'd NH_4Cl solution. The phases were separated and diluted with ether and the aqueous layer was washed with Et_2O. The combined organic solutions were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The product was purified by normal phase chromatography (100% hexanes to 10% EtOAc/Hexanes) to give the desired product.

Step B: 2-(2-chloroethyl)-2-phenylpent-4-enenitrile

In a 1L rb flask charged with 500mL of THF and N,N-di-*iso*-propylamine (29.94 mmol, 4.20 ml) at -78°C under nitrogen was added BuLi (2.5 M, 29.94 mmol, 11.98 ml) dropwise. The resultant clear colorless solution was stirred 10 minutes at -78°C, before a solution of 2-phenylpent-4-enenitrile (4.28 g, 27.11 mmol) in 10 mL THF was added via cannula (plus 5 mL rinse). The enolate (yellow/orange) was stirred at -78°C for 30 minutes at which time a solution of 1-bromo-2-chloro-ethane (40.83 mmol, 1.72 mmol) in 10 mL THF (plus 5 ml wash) was added dropwise, resulting in a blood red solution. The reaction was stirred at -78°C and then warmed to -40°C over 4 hours. The mixture was treated with an additional 1.5 equivalents of 1-bromo-2-chloroethane (3.4 ml) and warmed to 0°C over 1 hour. The reaction was quenched by the addition of 100 mL of sat'd NH_4Cl. The phases were separated and diluted with ether and the aqueous layer was washed with Et_2O. The combined organic solutions were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The product was purified by normal phase chromatography (100% hexanes to 10% EtOAc/Hexanes) to give a yellow oil.

Step C: tert-butyl 3-allyl-3-phenylpyrrolidine-1-carboxylate

A solution of LAH (1M, 10.9 mmol, 10.9 ml) in 20 mL THF at ambient temperature under N_2 was treated via canula with 2-(2-chloroethyl)-2-

phenylpent-4-enenitrile (1.6 g, 7.26 mmol) in 5mL THF (plus 5 mL rinse). The resultant yellow solution was stirred at ambient temperature for 2.5 days. The reaction was quenched by the dropwise addition of 1 mL of H_2O with the reaction on ice. The mixture was diluted with large volumes of 1N NaOH and Ether until the organic layers could be separated and the aqueous layer extracted. The combined organics were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was dissolved in 30 mL CH_2Cl_2 and 30 mL of sat. $NaHCO_3$ and treated with Boc_2O (10.9 mmol, 2.5 ml). The reaction stirred at ambient temperature overnight. The biphasic mixture was separated and extracted the $NaHCO_3$ layer with CH_2Cl_2. The combined organic solutions were washed with brine and the aqueous layer was back extracted with CH_2Cl_2. The combined organics were then dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by normal phase chromatography (0-10% EtOAc/Hexanes) to give a clear colorless oil.

Step D: tert-butyl 3-(2-oxoethyl)-3-phenylpyrrolidine-1-carboxylate

In a 25 mL flask containing tert-butyl 3-allyl-3-phenylpyrrolidine-1-carboxylate (236 mg, 0.821 mmol) and 10 mL of a 3:1 acetone/water mixture under N_2 at ambient temperature was added $NaIO_4$ (2.46 mmol, 527 mg), followed by a 2.5 wt% solution of OsO_4 (0.08 mmol, 22.2mg, 1ml) in 2-methyl-2-propanol (1mL). The chunky white/yellow mixture was diluted with more acetone and water and stirred at ambient temperature for 3 hours. The reaction was partitioned between H_2O and EtOAc and the aqueous layer was extracted with EtOAc (3x). The combined organic solutions were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by normal phase chromatography (5 to 20% EtOAc/Hexanes) to give a clear colorless oil.

Step E: tert-butyl 3-{2-[5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulen-12-yl]ethyl}-3-phenylpyrrolidine-1-carboxylate

Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with tert-butyl 3-(2-oxoethyl)-3-phenylpyrrolidine-1-carboxylate, the title compound was obtained.

Step F: 12-[2-(3-phenylpyrrolidin-3-yl)ethyl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene hydrochloride

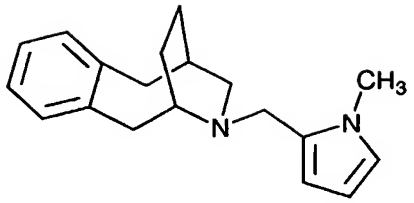
To a solution of tert-butyl 3-{2-[5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulen-12-yl]ethyl}-3-phenylpyrrolidine-1-carboxylate (105 mg, 0.228 mmol) in 1 mL CH_2Cl_2 was added 2 mL of 1 M HCl in diethyl ether. The resultant solution was stirred at ambient temperature overnight. The mixture was concentrated to dryness and dissolved in 2 mL of 1M HCl in diethyl ether with a small amount of MeOH to solubilize everything. The reaction stirred at ambient temperature over the weekend. Upon completion, reaction was concentrated *in vacuo* to give the desired product.

Step G: (6*S*,9*R*)-12-{2-[(3*R*)-1-benzoyl-3-phenylpyrrolidin-3-yl]ethyl}-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene and (6*S*,9*R*)-12-{2-[(3*S*)-1-benzoyl-3-phenylpyrrolidin-3-yl]ethyl}-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene

To a solution of 12-[2-(3-phenylpyrrolidin-3-yl)ethyl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene hydrochloride (50mg, 0.126 mmol) in 2 mL CH_2Cl_2 at ambient temperature under N_2 was added triethylamine (0.500 mmol, 70 ul) followed by benzoyl chloride (0.19 mmol, 20 ul). The resultant clear pale yellow solution was stirred overnight at ambient temperature. The reaction was quenched by the addition of satd. $NaHCO_3$ solution and diluted with EtOAc and the aqueous layer was extracted with EtOAc (3x). The combined organic solutions were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by normal phase chromatography (0-5% MeOH($5\%NH_4OH$)/CH_2Cl_2) to give the desired product. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{32}H_{37}N_2O$ ($M+H^+$): 465.2901. Found 465.2870.

EXAMPLE 76

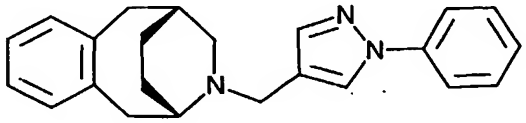
(6*S*,9*R*)-12-[(1-methyl-1*H*-pyrrol-2-yl)methyl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 1-methyl-1H-pyrrole-2-carbaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{19}H_{24}N_2$ ($M+H^+$): 281.2012. Found 281.1997.

EXAMPLE 77

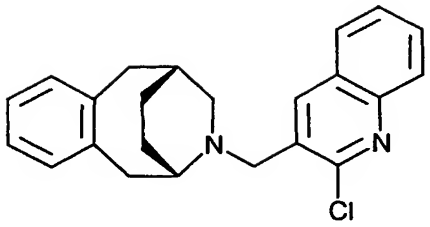
(6*S*,9*R*)-12-[(1-phenyl-1*H*-pyrazol-4-yl)methyl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 4-formyl-1-phenyl-1H-pyrazol-2-ium, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{23}H_{25}N_3$ ($M+H^+$): 344.2121. Found 344.2148.

EXAMPLE 78

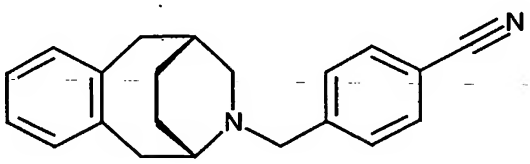
(6*S*,9*R*)-12-[(2-chloroquinolin-3-yl)methyl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 2-chloroquinoline-3-carbaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{23}H_{23}N_2Cl$ ($M+H^+$): 363.1623. Found 363.1607.

EXAMPLE 79

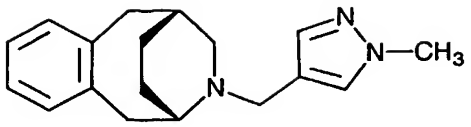
4-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulen-12-ylmethyl]benzonitrile



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 4-formylbenzonitrile, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{21}H_{22}N_2$ ($M+H^+$): 303.1856. Found 303.1849.

EXAMPLE 80

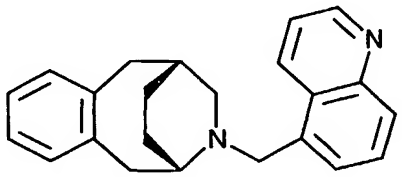
(6*S*,9*R*)-12-[(1-methyl-1*H*-pyrazol-4-yl)methyl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 1-methyl-1H-pyrazole-4-carbaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{18}H_{23}N_3$ ($M+H^+$): 282.1965. Found 282.1985.

EXAMPLE 81

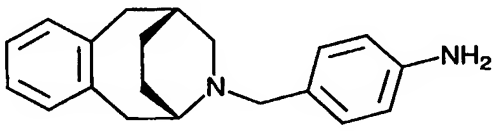
(6*S*,9*R*)-12-(quinolin-5-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with quinoline-5-carbaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{23}H_{24}N_2$ ($M+H^+$): 329.2012. Found 329.1991.

EXAMPLE 82

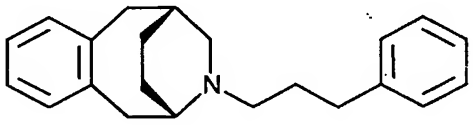
4-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulen-12-ylmethyl]phenylamine



Following the procedures described in Example 32 (Steps A and B), replacing 3-nitrobenzaldehyde of Step A with 4-nitrobenzaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08-7.11 (m, 4 H); 7.03 (m, 1 H); 7.00 (m, 1H); 6.63 (d, J = 8.1 Hz, 2 H); 3.66 (d, J = 1.29 Hz, 1 H); 3.58 (broad s, 2 H); 3.57 (d, J = 12.9 Hz, 1 H); 3.26 (m, 1 H); 3.20 (dd, J – 3.9, 14.2 Hz, 1 H); 3.07 (dd, J = 2.9, 14.9 Hz, 1 H); 2.87 (dd, J = 9.5, 14.2 Hz, 1 H); 2.76-2.81 (m, 2 H); 2.70 (dd, J = 7.8, 14.8 Hz, 1 H); 2.45 (m, 1 H); 1.75 (m, 1 H); 1.49 (m, 1 H): 1.23 (m, 1H); 1.12 (m, 1H). HRMS (ES) exact mass calculated for $C_{20}H_{26}Cl_2N_2$ ($M+H^+$): 293.2012. Found 293.2016.

EXAMPLE 83

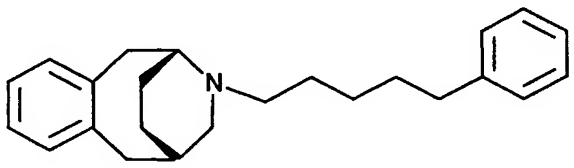
(6*S*,9*R*)-12-(3-phenylpropyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo [*a*][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 3-phenylpropanal, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{22}H_{27}N$ ($M+H^+$): 306.2216. Found 306.2231.

EXAMPLE 84

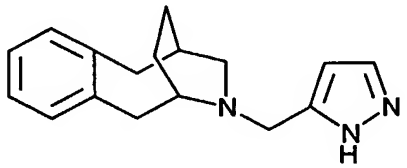
(6*R*,9*S*)-12-(5-phenylpentyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo [*a*][8]annulene



Following the procedures described in Example 1, replacing (6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene with (6*R*,9*S*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene and 3-bromobenzaldehyde of Step E with 5-phenylpentanal, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{24}H_{31}N$ ($M+H^+$): 334.2529. Found 334.2551.

EXAMPLE 85

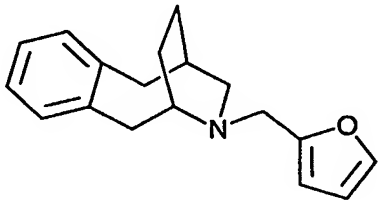
(6*S*,9*R*)-12-(1*H*-pyrazol-5-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 1H-pyrazole-5-carbaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{17}H_{22}N_3$ ($M+H^+$): 268.1808. Found 268.1811.

EXAMPLE 86

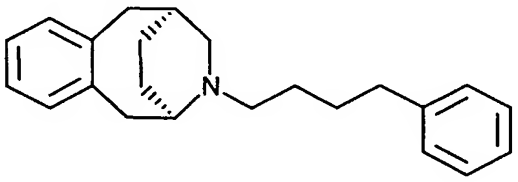
(6*S*,9*R*)-12-(2-furylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo [*a*][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 2-furaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{18}H_{22}NO$ ($M+H^+$): 268.1696. Found 268.1703.

EXAMPLE 87

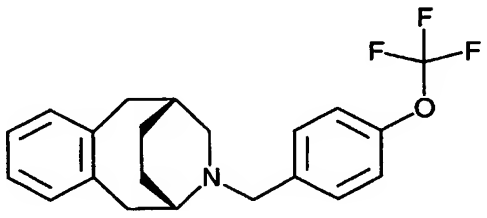
(6*R*,9*S*)-12-(4-phenylbutyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo [*a*][8]annulene



Following the procedures described in Example 1, replacing (6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene with (6*R*,9*S*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene and 3-bromobenzaldehyde of Step E with 4-phenylbutanal, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{23}H_{30}N$ ($M+H^+$): 321.2451. Found 321.2434.

EXAMPLE 88

(6*S*,9*R*)-12-[4-(trifluoromethoxy)benzyl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene

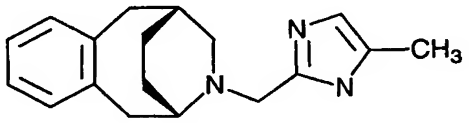


Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 4-(trifluoromethoxy)benzaldehyde, the title

compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{21}H_{22}NOF_3$ ($M+H^+$): 362.1726. Found 362.1698.

EXAMPLE 89

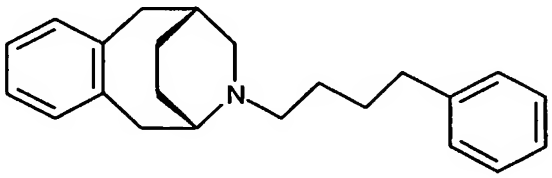
(6*S*,9*R*)-12-[(5-methyl-1*H*-imidazol-2-yl)methyl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 5-methyl-1H-imidazole-2-carbaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{18}H_{23}N_3$ ($M+H^+$): 282.1965. Found 282.1985.

EXAMPLE 90

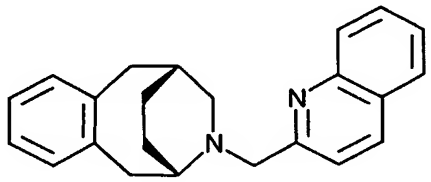
(6*S*,9*R*)-12-(4-phenylbutyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 4-phenylbutanal, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{23}H_{29}N$ ($M+H^+$): 320.2373. Found 320.2370.

EXAMPLE 91

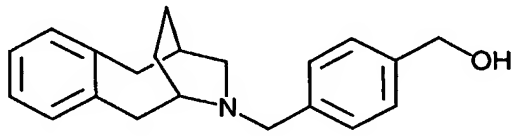
(6*S*,9*R*)-12-(quinolin-2-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with quinoline-2-carbaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{23}H_{24}N_2$ ($M+H^+$): 329.2012. Found 329.2001.

EXAMPLE 92

{4-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulen-12-ylmethyl]phenyl}methanol



Step A: 4-[5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulen-12-ylmethyl]benzaldehyde

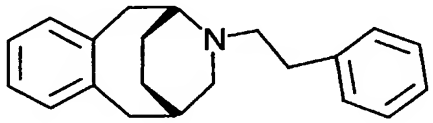
To a solution of (6*S*,9*R*)-12-(4-cyanobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene chloride, prepared following the procedures described for Example 79, in 1 ml of dry CH_2Cl_2 was added di-*iso*-butyl aluminum hydride (1M, 1.13 mmol, 1.13 ml). The reaction stirred at ambient temperature overnight. The mixture was cooled to 0°C and treated with MeOH (500 ul), MeOH/H_2O (1:1/1ml), and HCl (6M). The solution was extracted with CH_2Cl_2. The organic layer was washed with satd. aqueous $NaHCO_3$, brine, dried over Na_2SO_4, and concentrated *in vacuo* to give the desired product. Proton NMR for the product was consistent with the title compound. ESI+ MS: 308 [M+1].

Step B: {4-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8] annulen-12-ylmethyl]phenyl}methanol

To a 0°C solution of 4-[5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[a][8]annulen-12-ylmethyl]benzaldehyde (46 mg, 0.151 mmol) in 1 ml of MeOH was added $NaBH_4$ (0.15 mmol, 5.67 mg). The reaction stirred at 0°C for 1 hour. A second equivalent of $NaBH_4$ was added followed by a third equivalent after another 40 minutes. The mixture stirred for an additional 20 minutes. The reaction was quenched with 1 ml of H_2O and continued to stir at ambient temperature overnight. The mixture was partitioned between sat. aqueous $NaHCO_3$ and CH_2Cl_2 and separated. The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by normal phase HPLC (0.25-5% MeOH (10%NH_4OH) in CH_2Cl_2) to give the desired product. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{21}H_{26}NO$ ($M+H^+$): 308.2009. Found 308.1999.

EXAMPLE 93

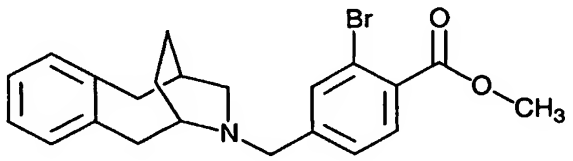
(6*R*,9*S*)-12-(2-phenylethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo [*a*][8]annulene



Following the procedures described in Example 1, replacing (6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene with (6*R*,9*S*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene and 3-bromobenzaldehyde of Step E with phenylacetaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{21}H_{25}N$ ($M+H^+$): 292.2060. Found 292.2071.

EXAMPLE 94

(methyl 2-bromo-4-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo [*a*][8]annulen-12-ylmethyl]benzoate



Step A: (6*S*,9*R*)-12-(3-bromo-4-carboxybenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene trifluoroacetate

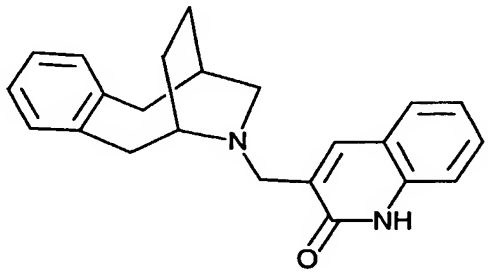
The 2-bromo-4-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulen-12-ylmethyl]benzonitrile (44mg, 0.115mmol), prepared following the procedures described in Example 60, was dissolved in acetic acid/conc. HCl (500 ul:500 ul) and heated to reflux overnight. LC/MS analysis showed some conversion to desired product. The reaction was treated with more conc. HCl and stirred at reflux for 3 days. The solution was concentrated *in vacuo*, taken up in acetonitrile and purified by reverse phase HPLC to give the desired product. Proton NMR for the product was consistent with the title compound. ESI+ MS: 400 [M] and 402 [M+2].

Step B: (methyl 2-bromo-4-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulen-12-ylmethyl]benzoate

Freshly prepared diazomethane was added dropwise to a solution of (6*S*,9*R*)-12-(3-bromo-4-carboxybenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epimino-methano)benzo[a][8]annulene trifluoroacetate (22 mg, 0.055 mmol) in 1 ml of CH_2Cl_2 at 0°C. The solution allowed to warm up to ambient temperature. When complete the reaction mixture was concentrated *in vacuo*, taken up in acetonitrile, and purified by reverse phase HPLC to give the desired product. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{22}H_{25}BrNO_2$ ($M+H^+$): 414.1082. Found 414.1063

EXAMPLE 95

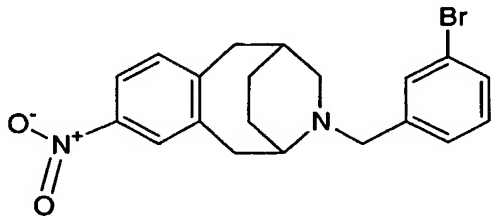
3-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulen-12-ylmethyl]quinolin-2(1H)-one



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 2-oxo-1,2-dihydroquinoline-3-carbaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{23}H_{24}N_2O$ ($M+H^+$): 345.1963. Found 345.1962.

EXAMPLE 96

12-(3-bromobenzyl)-3-nitro-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo [*a*][8]annulene

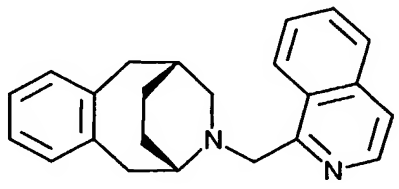


Following the procedures described in Example 48 (Steps A-D), the title compound was obtained. Proton NMR for the product was consistent with the title compound. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (dd, J = 2.4, 8.0 Hz, 1 H); 7.90 (d, J = 2.2 Hz, 1 H); 7.36 (app d, J = 7.8 Hz, 1 H); 7.26 (broad s, 1 H); 7.23 (d, J = 8.2 Hz, 1 H); 7.14 (t, J = 7.6 Hz, 1 H); 7.08 (app d, J = 7.6 Hz, 1 H); 3.70 (d, J = 13.7 Hz, 1 H); 3.61 (d, J = 13.7 Hz, 1 H); 3.28-3.32 (m, 2 H); 3.11 (dd, J = 4.6, 14.9 Hz, 1 H); 2.95 (dd, J = 7.8, 14.6 Hz, 1 H); 2.89 (dd, J = 7.2, 14.7 Hz, 1 H); 2.81 (dt, J = 10.7,

2.3 Hz, 1 H); 2.68 (dd, J = 3.7, 10.5 Hz, 1 H); 2.56 (m, 1 H); 1.90 (m, 1 H); 1.69 (m, 1 H); 1.44 (m, 1 H); 1.60 (m, 1 H). HRMS (ES) exact mass calculated for $C_{20}H_{22}BrN_2O_2$ ($M+H^+$): 401.0859. Found 401.0855.

EXAMPLE 97

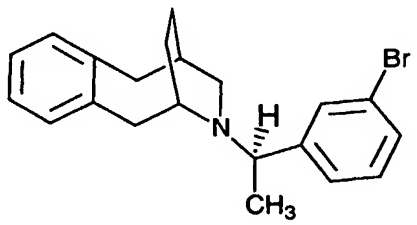
(6*S*,9*R*)-12-(isoquinolin-1-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with isoquinoline-1-carbaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{23}H_{24}N_2$ ($M+H^+$): 329.2012. Found 329.1991.

EXAMPLE 98

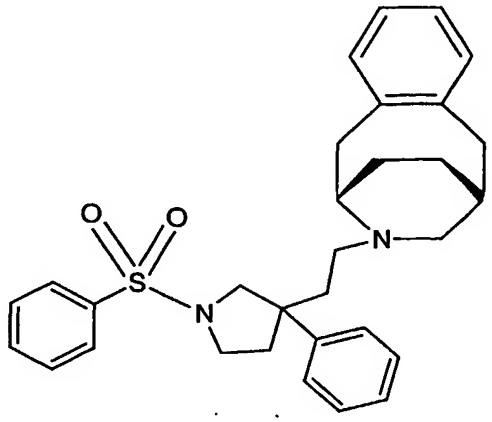
(6*S*,9*R*)-12-[(1*R*)-1-(3-bromophenyl)ethyl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene



Following the procedures described in Example 16, the title compound was obtained as the minor diastereomer. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{21}H_{25}BrN$ ($M+H^+$): 370.1165. Found 370.1164.

EXAMPLE 99

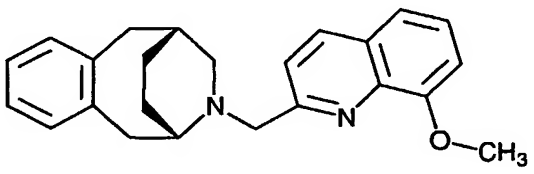
(6*S*,9*R*)-12-{2-[(3*R*)-3-phenyl-1-(phenylsulfonyl)pyrrolidin-3-yl]ethyl}-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene and (6*S*,9*R*)-12-{2-[(3*S*)-3-phenyl-1-(phenylsulfonyl)pyrrolidin-3-yl]ethyl}-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene



Following the procedures described in Example 77, Step G, but using benzene sulfonyl chloride in place of benzoyl chloride, the title compounds was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{31}H_{36}N_2O_2S$ ($M+H^+$): 501.2570. Found 501.2531.

EXAMPLE 100

(6*S*,9*R*)-12-[(8-methoxyquinolin-2-yl)methyl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene

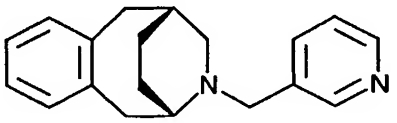


Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 8-methoxyquinoline-2-carbaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title

compound. HRMS (ES) exact mass calculated for $C_{24}H_{26}N_2O$ ($M+H^+$): 359.2118. Found 359.2099.

EXAMPLE 101

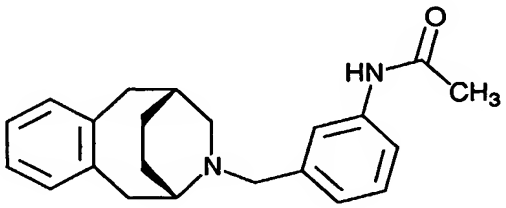
(6*S*,9*R*)-12-(pyridin-3-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with nicotinaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound.
HRMS (ES) exact mass calculated for $C_{19}H_{22}N_2$ ($M+H^+$): 279.1856. Found 279.1861.

EXAMPLE 102

N-{3-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulen-12-ylmethyl]phenyl}acetamide

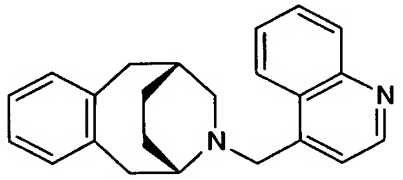


To 3-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8] annulen-12-ylmethyl]aniline (40mg, 0.137 mmol), prepared following the procedures described in Example 32 (Steps A and B), in CH_2Cl_2 (2 ml) were added pyridine (0.27 mmol, 20 ul) and acetyl chloride (0.27 mmol, 20 ul). After 6 hours, an additional 2 equivalents of pyridine and acetyl chloride were added and the reaction mixture stirred overnight. The reaction was quenched with MeOH and concentrated. The crude product was dissolved in ACN and purified by reverse phase HPLC to give

18.16 mg of desired product. Proton NMR for the product was consistent with the title compound. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, J = 7.5 Hz, 1 H); 7.23 (t, J = 7.5 Hz, 1 H); 7.06-7.15 (m, 4 H); 6.99-7.04 (m, 2 H); 3.73 (d, J = 13.5 Hz, 1 H); 3.65 (d, J = 13.5 Hz, 1 H); 3.27 (m, 1 H); 3.19 (dd, J = 5.5, 15.0 Hz, 1 H); 3.10 (dd, J = 4.5, 15 Hz, 1 H); 2.87 (dd, J = 8.5, 14.5 Hz, 1 H); 2.73-2.81 (m, 3 H); 2.46 (m, 1 H); 2.18 (s, 3 H); 1.84 (m, 1 H); 1.62 (m, 1 H); 1.36 (m, 1 H); 1.27 (m, 1 H). The product could be freebased (saturated bicarbonate/CH_2Cl_2). HRMS (ES) exact mass calculated for $C_{22}H_{26}N_2O$ ($M+H^+$): 335.2118. Found 335.2068.

EXAMPLE 103

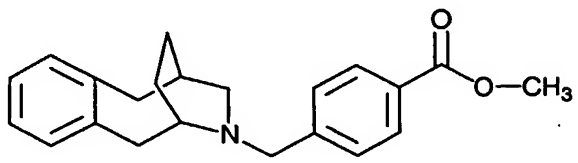
(6*S*,9*R*)-12-(quinolin-4-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo n[*a*][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with quinoline-4-carbaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{23}H_{24}N_2$ ($M+H^+$): 329.2012. Found 329.1992.

EXAMPLE 104

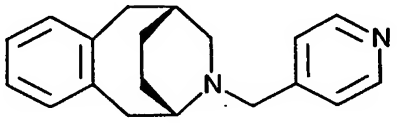
methyl 4-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulen-12-ylmethyl]benzoate



To a solution of (6*S*,9*R*)-12-(4-cyanobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene chloride (29 mg, 0.096 mmol), prepared following the procedures described in Example 79, in 500 ul of CH_2Cl_2 was added MeOH/HCl (1:1, 1ml). The reaction was heated to reflux and allowed to stir overnight. The mixture cooled to ambient temperature and was concentrated *in vacuo*. The residue was taken up in acetonitrile and purified by reverse phase HPLC to give the desired product. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{22}H_{26}NO_2$ ($M+H^+$): 336.1958. Found 336.1932.

EXAMPLE 105

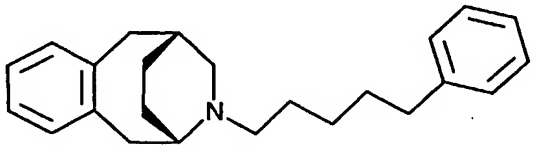
(6*S*,9*R*)-12-(pyridin-4-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo [*a*][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with isonicotinaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{19}H_{22}N_2$ ($M+H^+$): 279.1856. Found 279.1858.

EXAMPLE 106

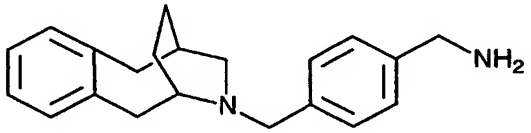
(6*S*,9*R*)-12-(5-phenylpentyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo [*a*][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 5-phenylpentanal, the title compound was obtained. Proton NMR for the product was consistent with the title compound. ESI+ MS: 334 [M+1]. HRMS (ES) exact mass calculated for $C_{24}H_{31}N$ ($M+H^+$): 334.2529. Found 334.2521.

EXAMPLE 107

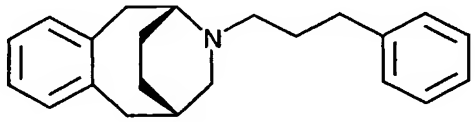
4-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulen-12-ylmethyl]benzylamine



A solution of (6*S*,9*R*)-12-(4-cyanobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene chloride (26 mg, 0.086 mmol), prepared following the procedures described in Example 79, in 2 ml of dry THF was cooled to 0°C under N_2. LAH in THF (1M, 0.13 mmol, 130 ul) was added and the solution stirred at 0°C for 5 hours and then at ambient temperature overnight. An additional amount of LAH (1M, 0.13 mmol, 130 ul) was added to the stirring reaction mixture at ambient temperature and continued stirring at ambient temperature for 5 hours. The reaction was quenched with ice water and extracted with CH_2Cl_2. The organic solution was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by normal phase chromatography (0.25%-8% MeOH ($10\%NH_4OH$)/CH_2Cl_2) to give the desired product. Proton NMR for the product was consistent with the title compound. ^1H NMR (500 MHz, $CDCl_3$) δ 7.23-7.28 (m, 4 H); 7.09-7.14 (m, 2 H); 7.00-7.11 (m, 2 H); 3.85 (s, 2 H); 3.27 (m, 1 H); 3.21 (dd, J = 4.4, 14.4 Hz, 1 H); 3.10 (dd, J = 3.2, 14.6 Hz, 1 H), 2.89 (dd, J = 9.3, 14.4 Hz, 1 H); 2.80 (m, 2 H); 2.72 (dd, J = 7.8, 14.9 Hz, 1 H); 42.46 (m, 1 H); 1.80 (m, 1 H); 1.52 (m, 1 H); 1.27 (m, 1 H); 1.16 (m, 1 H). HRMS (ES) exact mass calculated for $C_{21}H_{27}N_2$ ($M+H^+$): 307.2169. Found 307.2173.

EXAMPLE 108

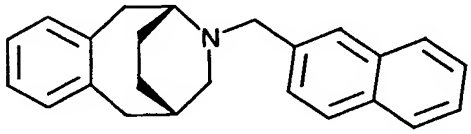
(6*R*,9*S*)-12-(3-phenylpropyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene



Following the procedures described in Example 1, replacing (6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene with (6*R*,9*S*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene and 3-bromobenzaldehyde of Step E with 3-phenylpropanal, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{22}H_{27}N$ ($M+H^+$): 306.2216. Found 306.2237.

EXAMPLE 109

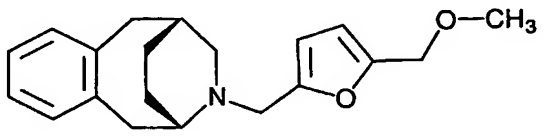
(6*R*,9*S*)-12-(2-naphthylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene



Following the procedures described in Example 1, replacing (6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene with (6*R*,9*S*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene and 3-bromobenzaldehyde of Step E with 2-naphthaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{24}H_{25}N$ ($M+H^+$): 328.2060. Found 328.2079.

EXAMPLE 110

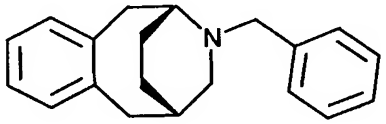
(6*S*,9*R*)-12-{[5-(methoxymethyl)-2-furyl]methyl}-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 5-(methoxymethyl)-2-furaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{20}H_{25}NO_2$ ($M+H^+$): 312.1958. Found 312.1971.

EXAMPLE 111

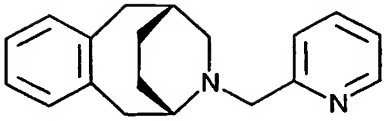
(6*R*,9*S*)-12-benzyl-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene



Following the procedures described in Example 1, replacing (6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene with (6*R*,9*S*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene and 3-bromobenzaldehyde of Step E with benzaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{20}H_{23}N$ ($M+H^+$): 278.1903. Found 278.1920.

EXAMPLE 112

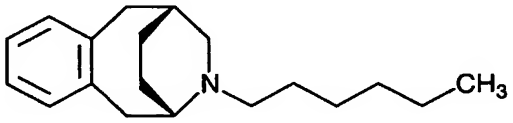
(6*S*,9*R*)-12-(pyridin-2-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with pyridine-2-carbaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{19}H_{22}N_2$ ($M+H^+$): 279.1856. Found 279.1856.

EXAMPLE 113

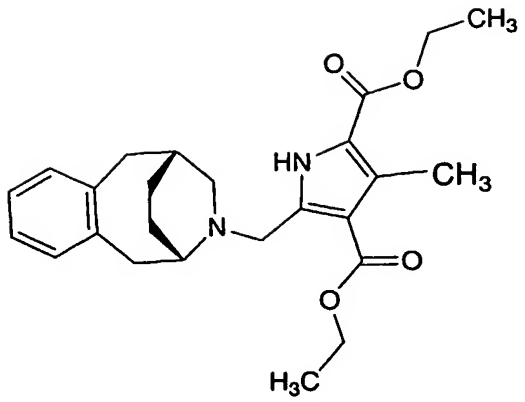
(6*S*,9*R*)-12-hexyl-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with hexanal, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{19}H_{29}N$ ($M+H^+$): 272.2373. Found 272.2375.

EXAMPLE 114

diethyl 5-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulen-12-ylmethyl]-3-methyl-1*H*-pyrrole-2,4-dicarboxylate



Step A: diethyl 5-formyl-3-methyl-1H-pyrrole-2,4-dicarboxylate

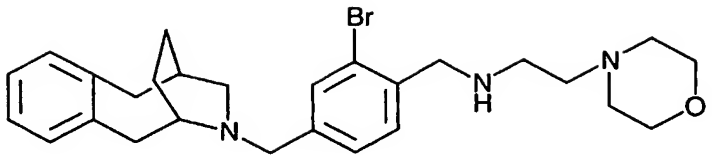
To a solution of diethyl 5-methyl-3-methyl -1H-pyrrole-2,4-dicarboxylate (5.00 g, 20.9 mmol) in THF (200 mL), AcOH (200 mL), and H_2O (200 mL) was added CAN (47.0 g, 85.7 mmol) in one portion. The reaction was stirred at ambient temperature for 4 hours, then poured into water (1000 mL) and extracted with CH_2Cl_2 (3 x 200 mL). The combined organic solutions were washed with saturated aqueous sodium bicarbonate (1 x 200 mL), dried over Na_2SO_4 and concentrated. Purification by flash chromatography (1-3% MeOH/CH_2Cl_2) gave a white solid (53.3 % yield).Elemental analysis calculated for $C_{12}H_{15}NO_5$: C: 56.91; H: 5.97; N: 5.53 Found: C: 56.98; H: 5.83; N: 5.44

Step B: diethyl 5-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulen-12-ylmethyl]-3-methyl-1*H*-pyrrole-2,4-dicarboxylate

Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with diethyl 5-formyl-3-methyl-1H-pyrrole-2,4-dicarboxylate, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{23}H_{24}N_2$ ($M+H^+$): 329.2012. Found 329.1984.

EXAMPLE 115

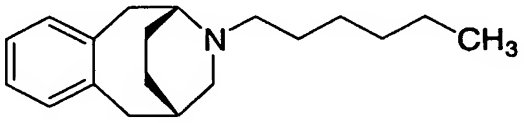
N-{2-bromo-4-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulen-12-ylmethyl]benzyl}-2-morpholin-4-ylethanamine



To a solution of 2-bromo-4-[5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[a][8]annulen-12-ylmethyl]benzaldehyde (29 mg, 0.11 mmol), prepared following the procedures described in Example 34 (Steps A-D), and 2-morpholin-4-ylethanamine in DCE (1 ml) was added Di-*iso*-propylethylamine (0.06 mmol, 10 ul). The reaction was stirred at ambient temperature under N_2 for 15 minutes, then $Na(OAc)_3BH$ (0.06 mmol, 12.3 mg) was added. The mixture stirred at ambient temperature overnight, then 1 ml of MeOH was added, and the solution was concentrated *in vacuo*. The residue was taken up in acetonitrile, filtered, and purified by reverse phase HPLC to give the desired product. Proton NMR for the product was consistent with the title compound. The product could be freebased (saturated bicarbonate/CH_2Cl_2). HRMS (ES) exact mass calculated for $C_{27}H_{37}BrN_3O$ ($M+H^+$): 498.2115. Found 498.2101.

EXAMPLE 116

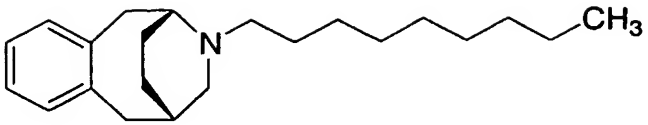
(6*R*,9*S*)-12-hexyl-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene



Following the procedures described in Example 1, replacing (6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene with (6*R*,9*S*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene and 3-bromobenzaldehyde of Step E with hexanal, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{19}H_{29}N$ ($M+H^+$): 272.2373. Found 272.2398.

EXAMPLE 117

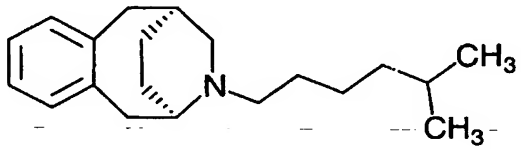
(6*R*,9*S*)-12-nonyl-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene



Following the procedures described in Example 1, replacing (6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene with (6*R*,9*S*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene and 3-bromobenzaldehyde of Step E with nonanal, the title compound was obtained. Proton NMR for the product was consistent with the title compound. ESI+ MS: 314 [M+1]. HRMS (ES) exact mass calculated for $C_{22}H_{35}N$ ($M+H^+$): 314.2843. Found 314.2866.

EXAMPLE 118

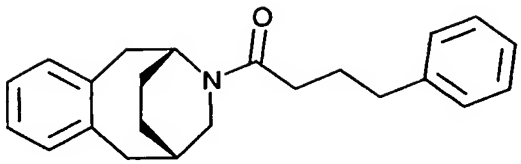
(6*R*,9*S*)-12-(5-methylhexyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo [*a*][8]annulene



Following the procedures described in Example 1, replacing (6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene with (6*R*,9*S*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene and 3-bromobenzaldehyde of Step E with 5-methylhexanal, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{20}H_{31}N$ ($M+H^+$): 286.2529. Found 286.2563.

EXAMPLE 119

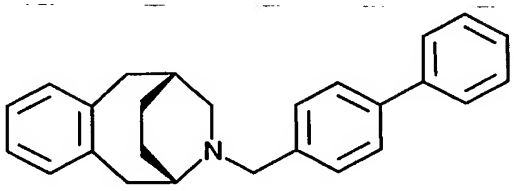
(6*R*,9*S*)-12-(4-phenylbutanoyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo [a][8]annulene



To a solution of (6*R*,9*S*)-5,6,7,8,9,10-hexahydro-6,9-(epimino-methano) benzo[*a*][8]annulene (20.0 mg, 0.1068 mmol) in 0.5 mL of DMF were added 4-phenylbutanoic acid (17.5 mg, 0.1068 mmol), EDC (24.6 mg, 0.1281 mmol), HOBT (17.3 mg, 0.1281 mmol), and di-*iso*-propylethylamine (55.8 uL, 0.3204 mmol). The resultant solution was stirred overnight at ambient temperature. The reaction was purified directly on a Gilson reverse phase HPLC, and the product containing fractions lyophilized to afford on oil which by NMR proved to be a 2.3:1 ratio of amide rotamers. HRMS (ES) exact mass calculated for $C_{23}H_{27}NO$ ($M+H^+$): 334.2166. Found 334.2168.

EXAMPLE 120

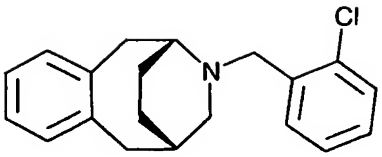
(6*S*,9*R*)-12-(1,1'-biphenyl-4-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 1,1'-biphenyl-4-carbaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{26}H_{27}N$ ($M+H^+$): 354.2216. Found 354.2241.

EXAMPLE 121

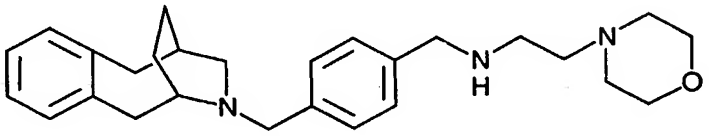
(6*R*,9*S*)-12-(2-chlorobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo [*a*][8]annulene



Following the procedures described in Example 1, replacing (6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene with (6*R*,9*S*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene and 3-bromobenzaldehyde of Step E with 2-chlorobenzaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{20}H_{22}ClN$ ($M+H^+$): 312.1514. Found 312.1516.

EXAMPLE 122

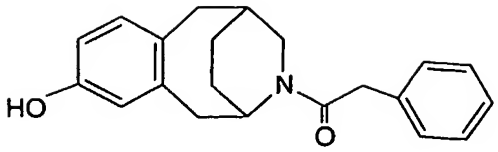
N-{4-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulen-12-ylmethyl]benzyl}-2-morpholin-4-ylethanamine



Following the procedures described in Example 115, replacing 2-bromo-4-[5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulen-12-ylmethyl]benzaldehyde with 4-[5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo [a][8]annulen-12-ylmethyl]benzaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{27}H_{38}N_3O$ ($M+H^+$): 420.3009. Found 420.2997.

EXAMPLE 123

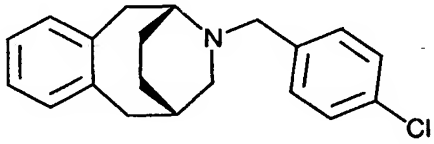
12-(phenylacetyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulen-2-ol



Following the Belanger et al. procedures, 2-hydroxy-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene chloride was obtained. Following the procedures described in Example 119, replacing (6*R*,9*S*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo [*a*][8]annulene with 2-hydroxy-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene chloride and 4-phenylbutanoic acid with phenylacetic acid, the title compound was obtained. Proton NMR for the product was consistent with the title compound.
TLC (15% MeOH/$CHCl_3$) R*f* = 0.5794.

EXAMPLE 124

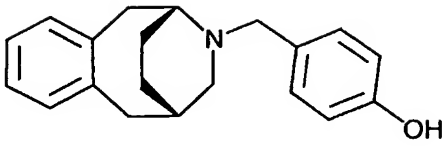
(6R,9S)-12-(4-chlorobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo [a][8]annulene



Following the procedures described in Example 1, replacing (6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene with (6*R*,9*S*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene and 3-bromobenzaldehyde of Step E with 4-chlorobenzaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{20}H_{22}ClN$ ($M+H^+$): 312.1514. Found 312.1518.

EXAMPLE 125

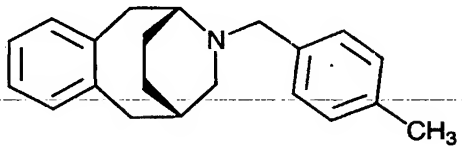
4-[(6*R*,9*S*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulen-12-ylmethyl]phenol



Following the procedures described in Example 1, replacing (6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene with (6*R*,9*S*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene and 3-bromobenzaldehyde of Step E with 4-hydroxybenzaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{20}H_{23}NO$ ($M+H^+$): 294.1853. Found 294.1874.

EXAMPLE 126

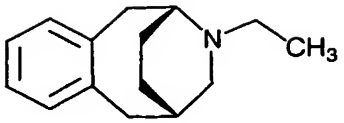
(6*R*,9*S*)-12-(4-methylbenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo [*a*][8]annulene



Following the procedures described in Example 1, replacing (6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene with (6*R*,9*S*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene and 3-bromobenzaldehyde of Step E with 4-methylbenzaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{21}H_{25}N$ ($M+H^+$): 292.2060. Found 292.2077.

EXAMPLE 127

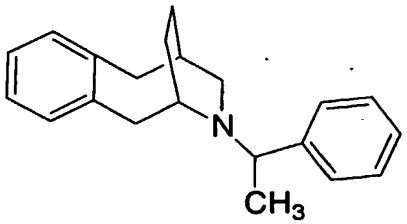
(6*R*,9*S*)-12-ethyl-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene



Following the procedures described in Example 1, replacing (6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene with (6*R*,9*S*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene and 3-bromobenzaldehyde of Step E with acetaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{15}H_{21}N$ ($M+H^+$): 216.1747. Found 216.1770.

EXAMPLE 128

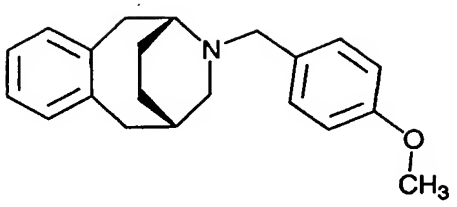
(6*S*,9*R*)-12-[(1*S*)-1-phenylethyl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene or (6*S*,9*R*)-12-[(1*R*)-1-phenylethyl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene



Following the procedures described in Example 16, replacing 3'-bromoacetophenone with 1-phenylethanone, the title compound was obtained. The diastereomers were isolated by HPLC (DeltaPak C-18, 30-100% MeOH/0.05% NH_4HCl_3, 60 ml/min). Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{21}H_{26}N$ ($M+H^+$): 292.2060. Found 292.2066.

EXAMPLE 129

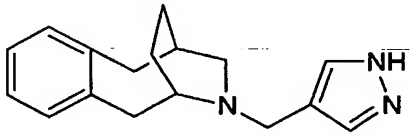
(6*R*,9*S*)-12-(4-methoxybenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene



Following the procedures described in Example 1, replacing (6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene with (6*R*,9*S*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene and 3-bromobenzaldehyde of Step E with 4-methoxybenzaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{21}H_{25}NO$ ($M+H^+$): 308.2009. Found 308.2037.

EXAMPLE 130

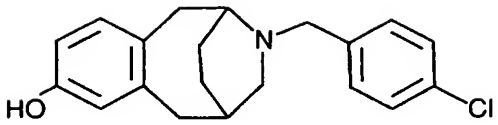
(6*S*,9*R*)-12-(1*H*-pyrazol-4-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 1H-pyrazole-4-carbaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{17}H_{22}N_3O$ ($M+H^+$): 268.1808. Found 268.1811.

EXAMPLE 131

12-(4-chlorobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo [*a*][8]annulen-2-ol

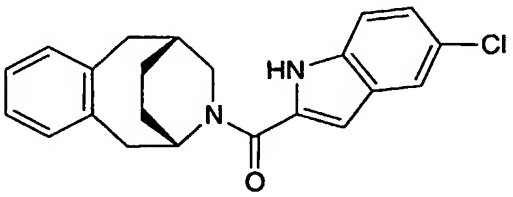


Following the Belanger et al. procedures, 2-hydroxy-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene chloride was obtained. Following the procedures described in Example 1, replacing 5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene of Step E with 3-hydroxy-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene and 3-bromobenzaldehyde of Step E with 4-chlorobenzaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound.
Elemental analysis calculated for $C_{20}H_{22}ClNO * HCl$

C: 64.35; H: 6.48; N: 3.75; Cl: 19.00
Found: C: 64.22; H: 6.36; N: 3.75; Cl: 19.01

EXAMPLE 132

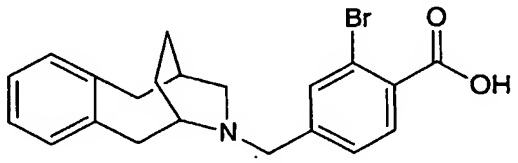
(6*S*,9*R*)-12-[(5-chloro-1H-indol-2-yl)carbonyl]-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene



Following the procedures described in Example119, replacing (6*R*,9*S*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo [*a*][8]annulene with (6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo [*a*][8]annulene and 4-phenylbutanoic acid with 5-chloro-1H-indole-2-carboxylic acid, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{22}H_{21}N_2OCl$ ($M+H^+$): 365.1415. Found 365.1350.

EXAMPLE 133

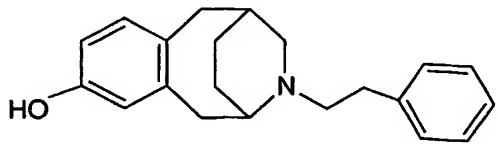
2-bromo-4-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8] annulen-12-ylmethyl]benzoic acid



Following the procedures described in Example 33 (Steps A-C), 2-bromo-4-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulen-12-ylmethyl]benzonitrile was obtained. This compound (44mg, 0.115 mmol) was dissolved in acetic acid/conc. HCl (500 ul: 500 ul) and heated to reflux overnight. LC/MS analysis showed some conversion to desired product. The reaction was treated with more conc. HCl and stirred at reflux for 3 days. The solution was concentrated *in vacuo*, taken up in acetonitrile and purified by reverse phase HPLC to give the desired product. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{21}H_{23}BrNO_2$ ($M+H^+$): 400.0907. Found 400.0902.

EXAMPLE 14

12-(2-phenylethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulen-2-ol



Following the Belanger et al. procedures, 2-hydroxy-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene chloride was obtained. Following the procedures described in Example 1, replacing 5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene of Step E with 3-hydroxy-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene and 3-bromobenzaldehyde of

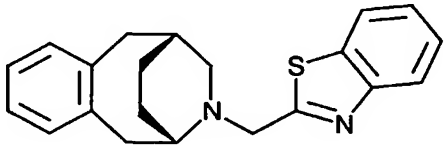
Step E with phenylacetaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound.
Elemental analysis calculated for $C_{20}H_{22}ClNO$ * HCl

C: 73.34; H: 7.62; N: 4.07; Cl: 10.30

Found: C: 70.00; H: 8.45; N: 3.21; Cl: 9.38

EXAMPLE 135

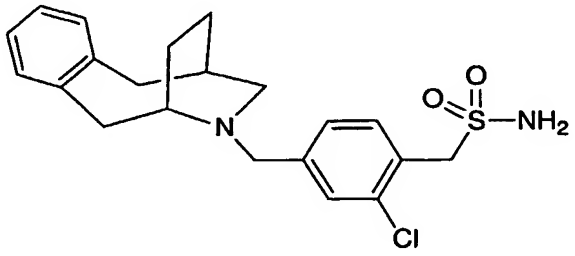
(6*S*,9*R*)-12-(1,3-benzothiazol-2-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 1,3-benzothiazole-2-carbaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{21}H_{22}N_2S$ ($M+H^+$): 335.1577. Found 335.1586.

EXAMPLE 136

1-{2-chloro-4-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulen-12-ylmethyl]phenyl}methanesulfonamide



Step A: Methyl 3-chloro-4-methylbenzoate

A solution of 3-chloro-4-methylbenzoic acid (5.17 g, 30.17 mmol)

in 90 mL MeOH was treated with the dropwise addition of acetyl chloride (20 mL, 30.2 mmol). Due to the resultant exotherm, the solution refluxed during the addition. After 2 hours, the reaction was concentrated *in vacuo* to afford a white solid. The NMR of the unpurified product was consistent with the desired methyl ester.

Step B: Methyl 4-bromomethyl-3-chlorobenzoate

To a solution of methyl 3-chloro-4-methylbenzoate (5.84 g, 30.17 mmol) in CCl_4 was added NBS (6.44 g, 36.20 mmol) followed by AIBN (495 mg, 3.02 mmol). The resultant solution was refluxed overnight, then cooled to ambient temperature and concentrated *in vacuo*. The residue was stirred with 20% EtOAc/ Hexanes, filtered, and concentrated *in vacuo* prior to purification on SiO_2 (15-30% CH_2Cl_2/hexanes) to afford two products determined by NMR and MS to be the dibromide and the desired monobromide.

Step C: Sodium *S*-[2-chloro-4-(methoxycarbonyl)benzyl] thiosulfate

To a solution of methyl 4-bromomethyl-3-chlorobenzoate (1.178 g, 4.49 mmol) in 10 mls of a 1:1 mixture of MeOH and H_2O was added sodium thiosulfate pentahydrate (1.115 g, 4.49 mmol). The resultant solution was refluxed for 1 hour prior to concentration *in vacuo* to afford a white solid which was clean by NMR.

Step D: Methyl 3-chloro-4-[(chlorosulfonyl)methyl]benzoate

Chlorine gas was bubbled through a solution of sodium *S*-[2-chloro-4-(methoxycarbonyl)benzyl] thiosulfate (350.8 mg, 0.833 mmol) in a 4:1 mixture of AcOH and water (total 5 mL) at 0°C slowly for 30 minutes. The reaction was then stirred for 1.5 hours during which time the yellow solution turned green and became heterogeneous. The mixture was partitioned between Et_2O and water. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo* and azeotroped with toluene (1X).

Step E: Methyl 4-[(aminosulfonyl)methyl]-3-chlorobenzoate

To a solution of unpurified methyl 3-chloro-4-[(chlorosulfonyl)methyl] benzoate in 5 mL of acetone at ambient temperature was added 5 mL of 10% NH_4OH in acetone. After 30 minutes, the reaction was concentrated *in vacuo* and the resultant residue purified on SiO_2 (1-3% MeOH/CH_2Cl_2) to afford a white solid which was pure by NMR.

Step F: 1-[2-Chloro-4-(hydroxymethyl)phenyl]methanesulfonamide

To a solution of methyl 4-[(aminosulfonyl)methyl]-3-chlorobenzoate (120 mg, 0.456 mmol) in 5 mL of THF at 0°C was added LAH (230 uL, 0.229 mmol). After 30 minutes, a second portion of LAH was added prior to warming the reaction to ambient temperature overnight. A third portion of LAH was added in the morning, and the reaction stirred for 30 minutes prior to the addition of EtOAc, then a satd. solution of NH_4Cl. The mixture was extracted with CH_2Cl_2 (4X), the combined organic layers dried over Na_2SO_4, and concentrated *in vacuo*. To afford a roughly 2:1 mixture of the benzyl alcohol and the starting ester by NMR.

Step G: 1-(2-Chloro-4-formylphenyl)methanesulfonamide

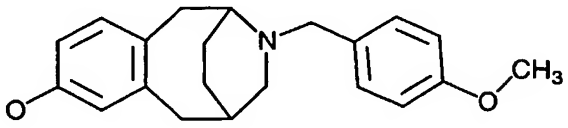
To a solution of 1-[2-chloro-4-(hydroxymethyl)phenyl] methanesulfonamide and its corresponding methyl ester (total <29 mg, <0.123 mmol) in 2 mL DMSO was added SO3-pyr (58 mg, 0.369 mmol), followed by Et_3N (85 uL, 0.615 mmol). After 30 minutes, the reaction was partitioned between EtOAc and a satd solution of NH_4Cl. The organic layer was separated and washed with brine (1X), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified through SiO_2 (50-100% EtOAc/CH_2Cl_2) to afford a yellow oil. Proton NMR for the product was consistent with the title compound.

Step H: 1-{2-chloro-4-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulen-12-ylmethyl]phenyl}methanesulfonamide

Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step A with 1-(2-chloro-4-formylphenyl)methanesulfonamide, the title compound was obtained. Proton NMR for the product was consistent with the title compound. ^1H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, J = 8.1 Hz, 1 H); 7.32 (s, 1 H); 7.18 (d, J = 7.8 Hz, 1 H); 7.11-7.17 (m, 2 H); 7.06 (dd, J = 2.2, 7.6 Hz, 1 H); 7.02 (app d, J = 6.1 Hz, 1 H); 4.48 (s, 2 H); 3.74 (d, 13.9 Hz, 1 H); 3.63 (d, 13.9 Hz, 1 H); 3.24 (m, 1 H); 3.17 (dd, J = 4.6, 14.4 Hz, 1 H); 3.06 (dd, J = 3.7, 14.6 Hz, 1 H); 2.89 (dd, J = 8.8, 14.4. Hz, 1 H); 2.72-2.79 (m, 3 H); 2.47 (m, 1 H); 1.83 (m, 1 H); 1.57 (m, 1 H); 1.35 (m, 1 H); 1.24 (m, 1 H). HRMS (ES) exact mass calculated for $C_{21}H_{25}ClN_2O_2S$ ($M+H^+$): 405.1398. Found 405.1388.

EXAMPLE 137

12-(4-methoxybenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulen-2-ol



Following the Belanger et al. procedures, 2-hydroxy-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene chloride was obtained. Following the procedures described in Example 1, replacing 5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene of Step E with 3-hydroxy-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene and 3-bromobenzaldehyde of Step E with 4-methoxybenzaldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound.

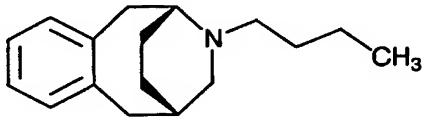
Elemental analysis calculated for $C_{21}H_{25}NO_2$ * HCl

C: 70.08; H: 7.28; N: 3.89; Cl: 9.85

Found: C: 70.24; H: 7.44; N: 3.75; Cl: 9.75

EXAMPLE 138

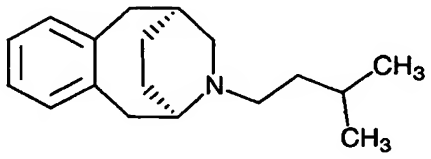
(6*R*,9*S*)-12-butyl-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene



Following the procedures described in Example 1, replacing (6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene with (6*R*,9*S*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene and 3-bromobenzaldehyde of Step E with butyraldehyde, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{17}H_{25}N$ ($M+H^+$): 244.2060. Found 244.2076.

EXAMPLE 139

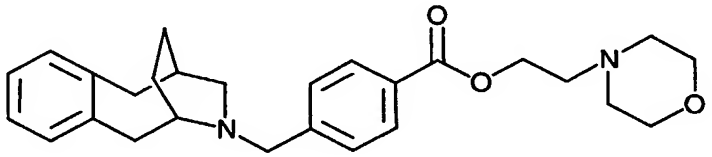
(6*R*,9*S*)-12-isopentyl-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8] annulene



Following the procedures described in Example 1, replacing (6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene with (6*R*,9*S*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene and 3-bromobenzaldehyde of Step E with 3-methylbutanal, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{18}H_{27}N$ ($M+H^+$): 258.2216. Found 258.2229.

EXAMPLE 140

2-morpholin-4-ylethyl 4-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulen-12-ylmethyl]benzoate



Step A: 4-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo [a][8]annulen-12-ylmethyl]benzoic acid

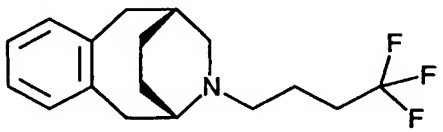
A solution of (6*S*,9*R*)-12-(4-cyanobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene chloride (27 mg, 0.089 mmol), prepared following the procedures described in Example 81, in acetic acid: conc. HCl (1:1/1ml) was heated to reflux and stirred overnight. The reaction allowed to cool to ambient temperature and was concentrated *in vacuo*. The crude product was dissolved in acetonitrile and purified by reverse phase HPLC to give the desired product. Proton NMR for the product was consistent with the title compound. ESI+ MS: 435 [M+1].

Step B: 2-morpholin-4-ylethyl 4-[(6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulen-12-ylmethyl]benzoate

To a solution of 4-[5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[a][8]annulen-12-ylmethyl]benzoic acid (9 mg, 0.03 mmol) and 4-(2-chloroethyl)morpholine (0.06 mmol, 8.4 mg) in DMF (500ul) was added $KHCO_3$ (0.14 mmol). The reaction stirred at ambient temperature overnight. LC/MS analysis indicated no reaction. The mixture was then heated to 60°C for 24 hours. An additional amount of 4-(2-chloroethyl)morpholine (0.075 mmol) and $KHCO_3$ (0.075 mmol) were then added and the reaction stirred at 60°C for 14 hours. The reaction was purified by reverse phase HPLC to give the desired product. ^1H NMR (500 MHz, CD_3OD, TFA salt) δ 8.14 (d, J = 8.3 Hz, 2 H); 7.71 (d, J = 8.3 Hz, 2 H); 7.13-7.23 (m, 4 H); 4.54 (t, J = 5.5 Hz, 2 H); 4.49 (s, 2 H); 3.90 (m, 1 H); 3.75 (m, 4 H); 3.55 (broad s, 2 H); 3.41 (m, 1 H); 3.31 (m, 1 H); 3.17 (dd, J = 10.0, 12.0 Hz, 1 H); 3.09 (dd, J = 2.2, 7.3 H, 1 H); 2.96 (broad s, 1 H); 2.75 (broad s, 4 H); 2.69 (broad s, 1 H); 1.87 (m, 1 H); 1.67 (m, 1 H); 1.43 (m, 1 H); 1.28 (m, 1 H)
The product could be freebased (saturated bicarbonate/CH_2Cl_2). HRMS (ES) exact mass calculated for $C_{27}H_{35}N_2O_3$ ($M+H^+$): 435.2642. Found 435.2629.

EXAMPLE 141

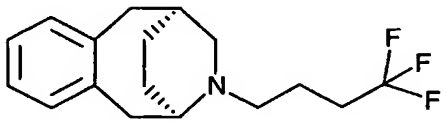
(6*S*,9*R*)-12-(4,4,4-trifluorobutyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene



Following the procedures described in Example 1, replacing 3-bromobenzaldehyde of Step E with 4,4,4-trifluorobutanal, the title compound was obtained. Proton NMR for the product was consistent with the title compound. ESI+ MS: 298 [M+1]. HRMS (ES) exact mass calculated for $C_{17}H_{22}NF_3$ ($M+H^+$): 298.1777. Found 298.1777

EXAMPLE 142

(6*R*,9*S*)-12-(4,4,4-trifluorobutyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano) benzo[*a*][8]annulene



Following the procedures described in Example 1, replacing (6*S*,9*R*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene with (6*R*,9*S*)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[a][8]annulene and 3-bromobenzaldehyde of Step E with 4,4,4-trifluorobutanal, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{17}H_{22}F_3N$ ($M+H^+$): 298.1777. Found 298.1792.

ASSAYS

The compounds of the instant invention described in the Examples above were tested by the assays described below and were found to have kinase inhibitory activity. In particular, the compounds of the instant invention inhibited IGF-1R or insulin receptor kinase activity with an IC_{50} of less than or equal to about 100 μM. Other assays are known in the literature and could be readily performed by those with skill in the art (see for example, Dhanabal *et al.*, *Cancer Res.* 59:189-197; Xin *et al.*, *J. Biol. Chem.* 274:9116-9121; Sheu *et al.*, *Anticancer Res.* 18:4435-4441; Ausprunk *et al.*, *Dev. Biol.* 38:237-248; Gimbrone *et al.*, *J. Natl. Cancer Inst.* 52:413-427; Nicosia *et al.*, *In Vitro* 18:538-549).

IGF-1R KINASE ASSAY

IGF-1R receptor kinase activity is measured by incorporation of phosphate into a peptide substrate containing a tyrosine residue. Phosphorylation of the peptide substrate is quantitated using anti-IGF-1R and anti-phosphotyrosine antibodies in an HTRF (Homogeneous Time Resolved Fluorescence) detection system. (Park, Y-W., et al. Anal. Biochem., (1999) 269, 94-104)

MATERIALS

IGF-1R RECEPTOR KINASE DOMAIN

The intracellular kinase domain of human IGF-1R was cloned as a glutathione S-transferase fusion protein. IGF-1R β-subunit amino acid residues 930 to 1337 (numbering system as per Ullrich et al., EMBO J. (1986) 5, 2503-2512) were cloned into the baculovirus transfer vector pAcGHLT-A (BD-Pharmingen) such that the N-terminus of the IGF-1R residues are fused to the C-terminus of the GST domain encoded in the transfer vector pAcGHLT-A. Recombinant virus was generated and the fusion protein expressed in SF-9 insect cells (BD-Pharmingen). Enzyme was purified by means of a glutathione sepharose column.

INSULIN RECEPTOR KINASE DOMAIN

The intracellular kinase domain of human insulin receptor was cloned as a glutathione S-transferase fusion protein. Insulin receptor β-subunit amino acid residues 941 to1343 (numbering system as per Ullrich et al., Nature, (1985) 313, 756-761) were cloned into the baculovirus transfer vector pAcGHLT-A (BD-Pharmingen) such that the N-terminus of the IGF-1R residues are fused to the C-terminus of the GST domain encoded in the transfer vector pAcGHLT-A. Recombinant virus was generated and the fusion protein expressed in SF-9 insect cells (BD-Pharmingen) Enzyme was purified by means of a glutathione sepharose column.

INSECT CELL LYSIS BUFFER

10mM Tris pH 7.5; 130mM NaCl; 2mM DTT; 1% Triton X-100; 10mM NaF; 10mM NaPi; 10mM NaPPi; 1X protease inhibitor cocktail (Pharmingen).

WASH BUFFER

Phosphate Buffered Saline (PBS): 137Mm NaCl, 2.6mM KCl, 10mM Na_2HPO_4, 1.8mM KH_2PO_4, pH 7.4; 1mM DTT; 1X protease inhibitor cocktail

DIALYSIS BUFFER

20mM Tris pH 7.5; 1mM DTT; 200mM NaCl; 0.05% Triton X-100 and 50% glycerol

ENZYME DILUTION BUFFER

50mM Tris pH 7.5; 1mM DTT; 100mM NaCl; 10% glycerol; 1mg/ml BSA

ENZYME REACTION BUFFER
20mM Tris pH 7.4; 100mM NaCl; 1mg/ml BSA; 5mM $MgCl_2$; 2mM DTT

QUENCH BUFFER
125mM Tris pH 7.8; 75mM EDTA; 500mM KF; 0.125% Triton X-100; 1.25% BSA; 60 nM SA-XL665 (Packard); 300 pM europium cryptate labeled anti-phosphotyrosine antibody (Eu-PY20)

PEPTIDE SUBSTRATE
Sequence LCB-EQEDEPEGDYFEWLE-NH_2; stock solution is 1mM disolved in DMSO; diluted to 1uM in 1X enzyme reaction buffer for 10X working stock. (LCB = aminohexanoylbiotin)

ATP
Stock solution is 0.5 M ATP (Boehringer) pH 7.4; stock solution is diluted to 40mM ATP in enzyme reaction buffer to give 20X working stock solution

HEK-21 CELL LINE
Human embryonic kidney cells (HEK-293) (ATCC) were transfected with an expression plasmid containing the entire IGF-1R coding sequence. After antibiotic selection, colonies were screened for IGF-1R overexpression by western blot analysis. One clone, designated HEK-21 was selected for cell based IGF-1R autophosphorylation assays.

HEK CELL GROWTH MEDIA
Dulbecco's Modified Eagle's Media (DMEM), 10% Fetal Calf Serum, 1X Penn/Strep, 1X Glutamine, 1X Non-essential amino acids (all from Life Technologies)

CELL LYSIS BUFFER
50mM Tris-HCl pH 7.4; 150mM NaCl; 1% Triton X-100 (Sigma); 1X Mammalian protease inhibitors (Sigma); 10mM NaF; 1mM NaVanadate

WESTERN BLOCKING BUFFER
20mM Tris-HCl pH 8.0; 150mM NaCl; 5% BSA (Sigma); 0.1% Tween 20 (Biorad)

METHODS

A. PROTEIN PURIFICATIONS

Spodoptera frugiperda SF9 cells were transfected with recombinant virus encoding either the GST-IGF-1R β-subunit or GST-InsR fusion protein at an MOI of 4 virus particles/cell. Cells are grown for 48 hours at 27°C, harvested by centrifugation and washed once with PBS. The cell pellet is frozen at –70°C after the final centrifugation. All subsequent purification steps are performed at 4°C. 10 grams of frozen cell paste is thawed in a 90ml volume of insect cell lysis buffer (BD-Pharmingen) and held on ice with occasional agitation for 20 minutes. The lysate is centrifuged at 12000g to remove cellular debris. Lysis supernatant was mixed with 45ml of glutathione agarose beads (BD-Pharmingen) and agitated slowly at 4°C for one hour after which the beads were centrifuged and washed 3X with wash buffer. The beads are resuspended in 45 ml of wash buffer and poured as a slurry into a chromatography column. The column is washed with 5 volumes of wash buffer and the GST-IGF-1R is eluted from the column with 5mM Glutathione in wash buffer. Pooled fractions are dialyzed vs. dialysis buffer and stored at -20°C.

B. IGF-1R KINASE ASSAY

The IGF-1R enzyme reaction is run in a 96 well plate format. The enzyme reaction consists of enzyme reaction buffer plus 0.1nM GST-IGF-1R, 100 nM peptide substrate and 2mM ATP in a final volume of 60 microliters. Inhibitor, in DMSO, is added in a volume 1 microliter and preincubated for 10 minutes at 22°C. Final inhibitor concentration can range from 100uM to 1nM. The kinase reaction is initiated with 3 microliters of 40mM ATP. After 20 minutes at 22°C, the reaction is stopped with 40 microliters of quench buffer and allowed to equilibrate for 2 hours at 22°C. Relative fluorescent units are read on a Discovery plate reader (Packard). IC50s for compounds are determined by 4 point sigmoidal curve fit.

C. INSULIN RECEPTOR KINASE ASSAY

The kinase reaction for insulin receptor is identical to that used to assay IGF-1R (above), except that GST-InsR is substituted at a final concentration of 0.1nM.

D. CELL BASED IGF-1R AUTOPHOSPHORYLATION ASSAY

IGF-1R inhibitor compounds are tested for their ability to block IGF-I induced IGF-1R autophosphorylation in a IGF-1R transfected human embryonic kidney cell line (HEK-21). HEK-21 cells over-expressing the human IGF-1R receptor are cultured in 6-well plates (37°C in a 5% CO_2 atmosphere) in HEK cell growth media to 80% of confluence. Cells are serum starved for four hours in HEK growth media with 0.5% fetal calf serum. A 10X concentration of inhibitor in growth media is added to the cells in one-tenth the final media volume and allowed to preincubate for one hour at 37°C. Inhibitor concentration can range from 10nM to 100uM. IGF-I (Sigma) is added to the serum starved cells to a final concentration of 30ng/ml. After a 10 minute incubation in the presence of IGF-I at 37°C, the media is removed, the cells washed once with PBS and 0.5mls of cold cell lysis buffer added. After 5 minutes incubation on ice, cells are scraped from the wells and lysis buffer plus cells are transferred to a 1.5ml microfuge tube. The total lysate is held at 4°C for twenty minutes and then centrifuged at top speed in a microfuge. The supernatant is removed and saved for analysis. Phosphorylation status of the receptor is assessed by Western blot. Lysates are electrophoresed on 8% denaturing Tris-Glycine polyacrylamide gels and the proteins transferred to nitrocellulose filters by electro-blotting. The blots are blocked with blocking reagent for 10 minutes after which anti-phosphotyrosine antibody (4G10, Upstate Biotechnology) is added to a final dilution of 1:1500. Blots and primary antibody are incubated at 4°C overnight. After washing with PBS plus 0.2% Tween 20 (Biorad), an HRP conjugated anti-mouse secondary antibody (Jackson Labs) is added at a dilution of 1:15000 and incubated at 4°C for 2 hours. Blots are then washed with PBS-Tween and developed using ECL (Amersham) luminescent reagent. Phosphorylated IGF-1R on the blots is visualized by autoradiography or imaging using a Kodak Image Station 440. IC50s are determined through densitometric scanning or quantitation using the Kodak Digital Science software.